

Exhibit H

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM
POWDER PRODUCTS MARKETING, SALES
PRACTICES AND PRODUCTS LIABILITY
LITIGATION

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

EXPERT REPORT OF MICHAEL BIRRER, MD, PHD
FOR GENERAL CAUSATION *DAUBERT* HEARING

Date: February 25, 2019


Michael Birrer, M.D., Ph.D.

BACKGROUND AND QUALIFICATIONS

Following is a brief summary of my background, education, medical training, clinical expertise and research activities.

I earned my undergraduate degree at Rensselaer Polytechnic Institute and graduated with a B.S. in Biology. I subsequently was accepted into the Medical Scientist Training Program at the Albert Einstein College of Medicine and completed my M.D. and Ph.D. in 1982 with my principal area of study in microbiology and immunology. I performed a medical internship at the Massachusetts General Hospital (MGH) and subsequently completed a residency in medicine at MGH. I entered the medical oncology fellowship at the National Cancer Institute (NCI) in Bethesda, Maryland and upon completion of that fellowship, performed a postdoctoral fellowship in the laboratory of Dr. John Minna on the molecular genetics of lung cancer. After completing my fellowship, I joined the faculty at the NCI in the Division of Cancer Treatment as an investigator in 1988. Three years later, I was appointed as a senior investigator (with tenure) and established the molecular mechanism section in the Division of Cancer Prevention and Control. Over the next 17 years, I held a number of positions, including member of the Committee for the Protection of Human Subjects, member of the Gynecologic Oncology Tumor Board, member of the Extramural Institutional Review Board (IRB), member of the Clinical Oncology Fellowship Section Committee, Chair of the Gynecologic Oncology Working Group in the Division of Clinical Sciences and Deputy Branch Chief of the Cell and Cancer Biology Branch.

In November 2008, I was appointed Professor of Medicine at the Harvard School of Medicine. I assumed the position of Director of Gynecologic Medical Oncology and the Gynecologic Oncology Research Program at MGH. This program integrated important new discoveries in translational research into clinical trials. In addition, I became the leader of the Dana Farber/Harvard Cancer Center Gynecologic Cancers program, one of 17 research programs in the DF/HCC. It had 76 members in 7 different institutes, more than \$12 million in National Institutes of Health (NIH) funding, and 50 active clinical trials.

In August 2017, I became the Director of the University of Alabama at Birmingham Comprehensive Cancer Center. This center was one of the original 8 comprehensive cancer centers designated in the United States in 1971 and has been continuously funded for 46 years. The Center has 410 members and more than \$100 million in cancer research funding. Recently, it has been named the O'Neal Comprehensive Cancer Center, with a gift of \$30 million.

I am recognized nationally and internationally as an expert in gynecologic oncology. I have published more than 380 peer-reviewed manuscripts, book chapters and review articles. I have served in leadership positions within the greater gynecologic oncology community. I have been the Chair and Chair Emeritus of the Department of Defense Ovarian Cancer Research Program, a program that awards between \$10 and \$20 million for ovarian cancer research. I have also served as the chair of the Committee for Experimental Medicine of the Gynecologic Oncology Group, the chair of the Gynecologic Cancer Steering Committee and chair of the Translational Science Working Group of the Gynecologic Cancer Intergroup, and most recently chair of the Core Correlative Science Committee of the NCI. I have been a member of the Society of Gynecologic Oncology (SGO), American Society of Clinical Oncology (ASCO),

American Association of Cancer Research and the International Gynecologic Cancer Society (IGCS) for 10-30 years. In this role, I served on the program committees of ASCO, SGO and IGCS.

My own research efforts have focused almost entirely on the molecular genetics of ovarian cancer. My laboratory has characterized the molecular events in the development of ovarian cancer. This has been supported by two Research Project Grants (RO1 grants). RO1 grants are the mainstay of funding for cancer research from the NIH. They are usually in the range of \$3-4 million. The laboratory has participated on the only UO1 grant for the early detection of ovarian cancer within the early detection research network (EDRN). UO1 grants are highly collaborative in nature, combining the expertise of several laboratories to tackle a major scientific/clinical problem. This work has involved the molecular characterization of early lesions of ovarian cancer. The results of this study will directly impact our understanding of the origins of this cancer. The laboratory is also a member of the Clinical Proteomic Tumor Analysis Consortium (CPTAC), which is dedicated to the characterization of cancers on the protein level. This effort will characterize the mechanisms for refractory ovarian cancer and involves multiple well-established laboratories with a budget of approximately \$7 million. Finally, I was awarded one of the RC4 stimulus grants (scored at 1% of all grants) focused on the genomics of ovarian cancer. These one-time grants provided up to \$5 million to answer big questions about clinically important tumors. The sum total of this is approximately \$34 million in funding and more than 20 years of effort focused on ovarian cancer research. My laboratory has helped define the molecular events in ovarian cancers of different histologies and tumor grade. We have defined both early and late genomic aberrations and are currently characterizing both early stage tumors and long-term survivors of ovarian cancer. The laboratory is one of the most knowledgeable in the world on the molecular biology of ovarian cancer and how it relates to the early development of the tumor and its clinical characteristics.

I am being compensated at a rate of \$400 per hour for my expert work in this litigation and \$1,000 per hour for time spent testifying.

Additional information concerning my credentials and scientific training and achievements can be found in my CV (attached as appendix A).

All of the opinions in this report are stated to a reasonable degree of scientific and medical certainty.

OVERVIEW AND SCOPE OF REPORT

I was asked to address the biological plausibility of plaintiffs' theory that the use of cosmetic talcum can cause ovarian cancer.

Biological plausibility is an important factor in the causation analysis because it assesses the etiology and mechanism(s) of a disease. Advanced tools and scientific knowledge enable researchers to more effectively understand the mechanisms of disease and demonstrate pathways from a purported exposure to the disease. Without an understanding of how a purported exposure can cause a disease, there can be no reliable statement of causation.

Part I of this report provides an overview of what is known about the origins of ovarian cancer, detailing recent molecular biology research, which has given us a clearer picture of the origin and progression of epithelial ovarian cancer. Part II addresses plaintiffs' experts' theories with respect to the supposed migration of talc to a woman's ovaries. Part III addresses what is known about talc and its theorized effects on a woman's ovaries. And Part IV addresses the methodological problems with the experiments of Dr. Saed, which we have now learned were funded by plaintiffs' counsel, and why the results of his experiments do not support the biological plausibility of plaintiffs' theory that perineal talc use can cause ovarian cancer.

I. OVARIAN CANCER

Epithelial ovarian cancer (OC) is a major health problem. It affects 22,000 women each year in the United States and produces 15,000 fatalities annually, making it one of the most lethal forms of cancer in women. The high mortality rate of OC is primarily due to its aggressive nature, as a result of which 75% of the diagnoses are at an advanced stage with the clinical presentation of widespread abdominal dissemination. OC therapy includes debulking surgery followed by taxol/platinum chemotherapy. It has been demonstrated that the residual disease after primary debulking surgery has a crucial impact on survivability. However, the limited overall survival is mainly due to the high rate of tumor relapse and the development of chemo-resistant disease.

A paradigm shift has occurred in our understanding of ovarian cancer. Ovarian cancer is no longer considered a single disease, but rather a composite number of unique cancers, characterized by completely different patterns of genomic alterations and different developmental origins.

The major histotypes of ovarian cancer include serous, endometrioid, clear cell and mucinous, while tumor grade extends from well differentiated (grade 1) through poorly differentiated (grade 3).¹ It has been well recognized that these tumors have different microscopic appearances, biologic characteristics and clinical features. Recent molecular discoveries have demonstrated that they are unique tumors with specific activated biochemical pathways. For high grade serous tumors, there is a profound abnormality in DNA repair. In the ordinary course, cells routinely sustain damage to DNA but employ a range of tools to repair such insults, including by causing cells that are beyond repair to die (to be replaced by healthy cells), a process called apoptosis. Serous tumors arise where this repair process is compromised by inactivating mutations in p53 and BRCA1/2. p53 and BRCA1/2 are genes that make sure the DNA is protected and mutations are corrected. Low grade serous cancers of the ovary differ from high grade serous cancers in that they have a high frequency of ras mutations with activation of the MAP kinase pathway and wild type p53. Ras mutations are very rare in high grade tumors while almost all of these tumors have p53 mutations.² Endometrioid ovarian cancers have mutations with the PI3 kinase pathway and CTNNB1, which are important genes that tell the

¹ Cannistra, *Cancer of the ovary*. N Engl J Med. (2004) 351(24):2519-29; Cho & Shih, *Ovarian cancer*. Annu Rev Pathol. (2009) 4:287-313.

² Cancer Genome Atlas Research Network, *Integrated genomic analyses of ovarian carcinoma*. Nature (2011) 474(7353):609-15.

cancer cell to grow or survive. Clear cell cancers have inactivating mutations in the tumor suppressor gene ARID1A, which is an important gene involved for maintaining the structure of the chromosome. Finally, mucinous tumors have activating mutations to ras, another signaling gene that protects the cell from the effects of chemotherapy.

The importance of these findings is that what we originally called ovarian cancer as a single disease is actually a collection of separate diseases. There is minimal molecular overlap among these tumors, which in part explains their diverse clinical presentations and natural histories. Gene expression profiling has also clearly demonstrated the distinct nature of ovarian tumors in relation to tumor histology and grade. These molecular discoveries have reinforced the view that ovarian cancer is actually a series of separate diseases with unique molecular features and different developmental origins.

It is now clear that a subset of clear cell and endometrioid cancers arise from endometriosis. Pathologic evidence has long showed these cancers in the presence of endometriosis and rare cases have described transition lesions. These cases show pathologic transition between benign endometriotic lesions to abnormal epithelial cells to ovarian cancer. More recent molecular data have confirmed this relationship by showing that the same mutation in ARID1A (an important mutation for the development of clear cell and endometriotic cancers of the ovary) can be found in the tumor and the adjacent endometriotic lesion. It is well accepted that these cancers arise from a process that transforms the endometriotic lesion.

In contrast, serous cancers of the ovary originate from a different tissue source and through a different process. High grade serous ovarian cancers arise primarily from the fallopian tube. Pathologic evaluation of fallopian tubes from prophylactic oophorectomies of BRCA 1/2 germ-line mutated patients revealed early invasive cancers in the fimbria and occasionally serous intraepithelial cancers (STICs). These latter lesions are entirely consistent with a precursor lesion for high grade serous ovarian cancer. Of interest, in addition to STICs, TP53 signatures are also found in the fallopian tubes. TP53 signatures are characterized by small collections of normal appearing fallopian tube epithelium (without any additional pathologic findings, including cellular inflammation), which stain for TP53. These strips of fallopian epithelium contain a mutated p53 gene (resulting in the accumulation of TP53), and it is likely some of these evolve into STICs and then into ovarian cancer.

The modern view of the molecular biology of ovarian cancer described above has important consequences both for our approach to the disease and also future research. Clearly, the molecular abnormalities and the pathways they affect will become important potential therapeutic targets, but also aid in early detection and the identification of prognostic biomarkers. Equally important, research that will move the field forward needs to recognize and incorporate the established features of the tumor described above. **This means utilizing appropriate cell lines and *in vivo* models to fit the research question being tested.** For example, utilizing a clear cell cancer cell line to test questions about HGSOC is of little value. Likewise, testing a particular hypothesis in ovarian cancer without *in vivo* experiments is unlikely to yield important data and meaningful discoveries. In all events, inquiries into the causes of one type of ovarian cancer may tell us nothing at all about the causes of another type of ovarian cancer because of the distinct pathways through which these diseases develop.

II. MIGRATION

A. General Observations

Plaintiffs' experts opine that it is accepted in the scientific community that talc can migrate to the ovaries from the perineum and/or through inhalation. Generally speaking, plaintiffs' experts' reports rely on two lines of supposed evidence to support this assumption: 1) the claimed presence of talc particles in ovaries and/or ovarian cancer tissue; and 2) experimental results attempting to demonstrate the transition of particles from the vagina up to the ovary. A closer investigation of the science, however, shows that plaintiffs' experts are significantly misinterpreting the findings of these articles and exaggerating their importance.

i. Supposed Presence Of Talc In Ovaries

The proposed finding of talc particles in ovarian cancers rests primarily on three publications, all of which have severe limitations. As explained further in this sub-section: (1) the first study used improper methods to identify talc and may have been tainted by contamination; (2) the second study found talc in a lymph node – not ovaries; and (3) the third study found talc in women's ovaries who had not used talc perineally and therefore says absolutely nothing about perineal talc use. To conclude based on these three studies that talc reaches the ovaries and therefore can cause ovarian cancer is speculative and highly misleading.

Talc and Carcinoma of the Ovary and Cervix by Henderson et al. (1971)³ reports the incidence of talc particles in a series of ovarian and cervical cancers. They report that 75% (10/13 patients) of the ovarian cancer tumors had talc particles, as did 5/12 normal ovaries from breast cancer patients. The talc was identified only by electron microscope (EM), which is not the standard analysis done now. The newer standard uses several different technologies, which increases the likelihood of finding rare particles of talc. Thus, it is difficult to credit the talc particle counts and uncertain whether talc was actually more prevalent in the ovarian cancer patients. The paper provides insufficient description as to the techniques used to gather the tissue and process it. Given the high frequency in the control specimens (breast cancer patients), laboratory contamination has to be a major concern. Although this study is cited by at least ten of plaintiffs' experts to support the theory that talc is present in women with ovarian cancer,⁴ it does not support their opinions because their methods were not reliable, and any talc may have resulted from contamination. And of course, the paper certainly does not support the theory that such presence of talc – even if true – causes ovarian cancer.

Cramer et al., *Presence of Talc in Pelvic Lymph Nodes of a Woman with Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc* (2007)⁵ reports a single case of a

³ Henderson et al., *Talc and carcinoma of the ovary and cervix*. J Obstet Gynaecol Br Commonw. (1971) 78(3):266-72.

⁴ Saed Rep. at 12; Smith-Bindman Rep. at 13, 35; Kane Rep. at 13, 14, 16; McTiernan Rep. at 58, 63; Carson Rep. at 4; Clarke-Pearson Rep. at 4, 8; Kessler Rep. at 23; Blair Smith Rep. at 16; Wolf Rep. at 5, 11; Plunkett Rep. at 26, 33, 49, 60; Moorman Rep. at 33; Singh Rep. at 18, 57.

⁵ Cramer et al., *Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc*. Obstet Gynecol. (2007) 110(2 Pt 2):498-501.

woman with ovarian cancer, a history of talc use and the identification of talc within a lymph node. The talc was identified by polarized light microscopy, scanning EM and x-ray spectroscopy. This report adds little support to the migration argument. It is a single case (despite a discussion of 12 other cases, there are no data presented on them), and the talc is found in the lymph node. There are no hypotheses on ovarian cancer arising from a process in the lymph node, and it is difficult to imagine talc reaching the ovary via the lymph system because the lymph system drains the abdomen and does not flow into it. Dr. McTiernan claims this study “demonstrate[s] talcum powder products can migrate from the perineal area to the ovaries and fallopian tube through both genital tract migration and inhalation.”⁶ A single case report cannot conclude anything and more importantly, it is essentially irrelevant because lymphatic spread is not thought to have any relevance to the origin of ovarian cancer.

The third study may provide the best explanation for the results of the other two. This 1996 study by Heller et al., entitled *The relationship Between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden*⁷ is a study of 24 patients who underwent oophorectomies and were interviewed pertaining to talc usage (12 of whom reported high talc use and 12 of whom reported never using talc). Talc particles were detected in the ovaries of all 24 cases regardless of exposure. While the authors explain this finding by implicating diaper use for the source of talc, there is no direct evidence for this at all. This explanation also does not make sense because the mean age of the women in the study was 49, meaning that the talc would have had to travel to the ovaries in their infancy and remain lodged there for decades. By contrast, the finding of talc in non-talc users is plausibly consistent with environmental contamination of operative specimens, either in the operating room or pathology suite. Although the authors mention examining solutions for the presence of talc, there is no detailed description about how they did it and specifically which solutions were tested. There are also many potential sources of talc that could be contaminants and no description of talc control methodology to ensure the operating rooms and pathology suites were free of talc. The evaluation of control tissues is absolutely critical to these types of studies. In this study, there are no controls, i.e., abnormal or normal tissues (other than the female genital tract) that would not be expected to have talc. The presence of talc in such control tissues would further support contamination. Dr. Smith-Bindman (along with several other plaintiffs’ experts) cites this study to support the proposition that talc migrates up the fallopian tubes and thereby plays a role in the development of ovarian cancer.⁸ As described above, however, talc particles were detected in every case **regardless of history of exposure**; there is no detailed description about how the authors examined solutions for the presence of talc; and the study lacked any control. If anything, this study suggests that talc found in a woman’s ovarian tissue bears no relation to perineal talc use.

⁶ McTiernan Rep. at 59. At least eight other experts also rely on this study. Saed Rep. at 12; Kane Rep. at 4, 14; Siemiatycki Rep. at 65; Wolf Rep. at 11; Zelikoff Rep. at 14; Plunkett Rep. at 29; Moorman Rep. at 33; Singh Rep. at 18, 20, 57.

⁷ Heller et al., *The relationship between perineal cosmetic talc usage and ovarian talc particle burden*. Am J Obstet Gynecol. (1996) 174(5):1507-10.

⁸ Smith-Bindman Rep. at 35. Several other experts likewise rely on this study for that proposition, including Kane Rep. at 14, 30; McTiernan Rep. at 29, 58, 59); Carson Rep. at 6; Clarke-Pearson Rep. at 8; Siemiatycki Rep. at 65; Wolf Rep. at 11; Zelikoff Rep. at 19; Plunkett Rep. at 28, 29, 35); Moorman Rep. at 33; Levy Rep. at 13, Singh Rep. at 18, 20, 57.

ii. Hypothesized Migration of Talc to Ovaries

The second line of evidence relied on by plaintiffs' experts are studies that supposedly support the theory that talc applied perineally can enter the vagina, travel through the cervix and endometrium and then travel up through the fallopian tube to the ovary. Not surprisingly, there are no studies that validate this theory, which is contrary to basic anatomy and common sense. Instead, the studies relied on by plaintiffs' experts either did not involve talc and/or involve the actual insertion of materials inside a woman's body, rather than dusting the outside of her body. These include the following:

1. Venter et al., *Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries* (1979).⁹ (This study is cited by the following plaintiffs' experts: Smith-Bindman (page 35), Kane (page 14), McTiernan (pages 58, 59), Carson (page 7), Clarke-Pearson (page 8), Siemiatycki (page 65), Wolf (page 11), Zelikoff (pages 12, 13), Plunkett (pages 28, 31).) The authors studied the migration of radionucleotide labelled human albumin microspheres as a model for talc in humans. They report 9 out of 21 patients demonstrated radioactivity in tubes and ovaries at the time of surgery. This study has serious methodologic flaws. First, the authors used the Tc-labelled human albumin microspheres as a surrogate for talc. It is well known that the radiolabels can disassociate from the protein (albumin) or that the protein can break down. Thus, the tracer (which produces the radioactivity) can travel separately and extensively compared to the whole complex. There are no controls for this at all in the study. Second, the study design necessitated putting the patients in a supine (lying-down) position with the buttocks slightly elevated and after injection kept like this for 2 hours with the legs pressed together. This is obviously not equivalent to dusting the groin with powder in a woman in the vertical position. Finally, it is impossible to determine from the study the exact level of radioactivity detected in the organs or for that matter, the blood. There are no numbers provided. Plaintiffs' experts' reliance on this study is flawed because the study does not eliminate the possibility that the radioactivity has broken off from the larger particle and traveled through the body in a mode completely different from direct migration up the fallopian tube. Moreover, there are no data in this study as to the frequency of disassociation of the isotope for albumin, its circulation or its distribution within the body.
2. Sjösten et al., *Retrograde migration of glove powder in the human female genital tract* (2004).¹⁰ (This study is cited by Smith-Bindman (pages 1, 35), McTiernan (page 59), Carson (page 7), Clarke-Pearson (page 8), Blair Smith (page 16)), Wolf (page 11), Plunkett (pages 28, 36), Zelikoff (page 12), Moorman (page 33) and Singh (pages 18, 19, 20, 57).) This study reports increased glove powder in the cervix, tubes and uterus in patients who had been exposed to gloves with powder compared to those exposed to gloves without powder. Although Dr. Clarke-Pearson, for example, cites this study as

⁹ Venter & Iturralde, *Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries*. S Afr Med J. (1979) 55(23):917-9.

¹⁰ Sjösten, Ellis & Edelstam, *Retrograde migration of glove powder in the human female genital tract*. Hum Reprod. (2004) 19(4):991-5.

supporting his retrograde migration theory, there are important and serious limitations of this study in relation to the present litigation. First, the study involved starch, not talc preparations. There are well documented differences both in physical size and biochemical properties between talc and starch that make these comparisons irrelevant. Second, the delivery of starch particles in this set of experiments is from bimanual exams using powdered gloves. This approach delivers the foreign bodies at the cervical OS with considerable intravaginal pressure, which, again, is quite different from perineal dusting.

3. Egli et al., *The transport of carbon particles in the human female reproductive tract* (1961).¹¹ (This study is cited by Zelikoff (page 13), Smith-Bindman (page 35), Kane (page 14), McTiernan (page 58), Carson (page 7), Clarke-Pearson (pages 7, 8), Blair Smith (page 16), Wolf (page 10), Zelikoff (page 13), Plunkett (pages 28-30) and Singh (pages 15, 60).) This study researched the mechanism by which spermatozoa reaches the oviduct in mammals by using carbon particles in humans as a model. A solution of dextran and bone black (carbon particles) was deposited into the distal vagina near the cervix in anesthetized women in the lithotomy position while an intramuscular injection of oxytocin was given. The patients then underwent the planned surgical procedure and the removed tubes were flushed with saline in an attempt to detect the carbon particles. Contrary to plaintiffs' experts' reliance on this study, there are many aspects of this study that limit its relevance and scientific value. First, there are no data presented to ensure that carbon particles are equivalent to talc in size and physical properties. Second, the patients were injected with oxytocin, a hormone known to induce muscular contraction within the female genital tract prior to general anesthesia. These are not conditions consistent with genital dusting in a standing female. Dr. Ellen Blair Smith emphasizes that "no propulsive force of talc was used in the study."¹² But this emphasis ignores the fact that carbon particles were placed in the posterior fornix of the vagina while the woman was under anesthesia, in the lithotomy position, and before being injected with oxytocin. Such a highly contrived model system tells us nothing of relevance to the dusting of the perineum with powder.
4. Kunz, et al., *The Uterine Peristaltic Pump* (1997).¹³ (This study is cited by Saed (page 12), Wolf (page 11) and Plunkett (pages 28, 35, 36, 37); it was also considered but not cited by Carson (ex. B), Clarke-Pearson (ex. B), Blair Smith (ex. C), Zelikoff (ex. B), Levy (ex. B) and Smith-Bindman (reliance list).) The first part of this study utilizes vaginal sonography to detect uterine contractions during the female menstrual cycle. This obviously measures changes in the uterine wall (via contractions) with an indirect interpretation of endometrial cavity pressure and therefore is not a direct measurement. In addition, there are no data presented to determine the direction of the pressure generated by the uterine wall contraction. Further, the act of transvaginal manipulation itself can certainly affect uterine contraction activity. That is assumed from the results of the

¹¹ Egli & Newton, *The transport of carbon particles in the human female reproductive tract*. *Fertil Steril*. (1961) 12:151-5.

¹² Smith Rep. at 16.

¹³ Kunz et al., *The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract*. *Adv Exp Med Biol*. (1997) 424:267-77.

second part of the study. The second methodology used was hysterosalpingoscintigraphy utilizing technetium-labelled albumin macrospheres of the same approximate size of human spermatozoa. Obviously, there are major differences between the macrospheres and human spermatozoa, not the least being the motility of spermatozoa and its entirely different biochemical composition, as described above. This study has a series of problems, including the use of radiolabeled albumin spheres, which can dissociate from the isotope, and the fact that the placement of these spheres into the reproductive tract of women is fundamentally different from dusting the perineum.

B. Additional Methodological Flaws In Plaintiffs' Experts' Opinions Regarding Migration Of Talc To The Ovaries

There are several additional methodological flaws in plaintiffs' experts' opinions regarding the migration of talc to the ovaries.

Dr. Clarke-Pearson – Dr. Clarke-Pearson analogizes to the migration of sperm into the tubes after coitus. It is rather surprising to hear this from a gynecological oncologist. The obvious difficulty with this line of reasoning is the fact that spermatozoa are motile and have evolved over millions of years to be able to migrate under their own control to increase the potential to fertilize the egg. This mode of transport is not consistent with a talc particle. Further, it should not need to be pointed out that the sperm is being delivered with considerable force and pressure at the cervical OS during the act of coitus rather than dusting on the surface of the perineum.

Dr. Smith-Bindman – In addition to relying on the studies set forth above, Dr. Smith-Bindman also claims that epidemiology data showing a reduced risk for ovarian cancer in women who underwent a tubal ligation is evidence for the role of talc in the development of ovarian cancer. This opinion, too, is not supported by the science. I note at the outset that while Dr. Smith-Bindman repeatedly asserts that studies show that the risk of ovarian cancer in talcum powder users is reduced in women who have undergone tubal ligation and hysterectomy,¹⁴ she does not cite any studies that support this claim.

There are studies that suggest a *generally* protective effect of tubal ligation, but there is no evidence that this effect is related to the blockage of transition of some agent through the fallopian tube. In fact, a number of studies have concluded that tubal ligation and/or hysterectomy has no effect on ovarian cancer risk in women who use talc perineally. For example, a study by Gertig et al. – the only cohort study that addressed the effect of tubal ligation and/or hysterectomy and the occurrence of ovarian cancer – concluded that “no effect modification was seen by history of tubal ligation.”¹⁵ A pooled study by Terry et. al. found that “exposure to genital powder applications that occurred before tubal ligation or hysterectomy

¹⁴ Smith-Bindman Rep. at 15, 35.

¹⁵ Gertig et al., *Prospective study of talc use and ovarian cancer*. J Natl Cancer Inst. (2000) 92(3):249-52.

made no substantive difference in the results.”¹⁶ There have also been case-control studies that have concluded that there was a lower incidence of ovarian cancer in talc users who had tubal ligation, but not for patients who had hysterectomies. For example, Cramer et al. (1999) found odds ratios of 0.98 and 1.80 for tubal ligation/no tubal ligation and 2.61 and 1.60 for hysterectomy/no hysterectomy¹⁷; and Mills et al. noted odds ratios of 0.88 and 1.54 for tubal ligation/no tubal ligation and odds ratios of 1.79 and 1.33 for hysterectomy/no hysterectomy.¹⁸ This is inherently illogical, since either procedure would cut off plaintiffs’ theorized pathway for talc migration. As such, the support for a theory by which the protective effect of tubal ligation can be attributed to shielding the ovaries from talc is lacking.

Notably, recent data have demonstrated that there are dramatic effects on the cells at the distal end of the fallopian tube cells after a tubal ligation.¹⁹ Given the role of the fimbria in the development of the majority of ovarian cancers, the demonstration of substantial development of quiescence cells in this region is highly relevant. It is likely that these cells cannot be transformed into cancer cells in this state. Thus, the effects of tubal ligation are likely related to biologic effects on the epithelial cells within the fallopian tube, which in turn decreases the number of cells that are potential precursors for ovarian cancer – and not to the elimination of a pathway for cancer initiators or promoters that ostensibly travel up the fallopian tubes toward the ovaries.

Dr. Wolf – In addition to the studies discussed above, and the sperm analogy, which is contrary to basic human biology, Dr. Wolf also invokes retrograde menstruation as evidence that talc could travel to the ovaries.²⁰ But retrograde menstruation is a different process; it occurs more closely to the fallopian tubes than does perineal dusting, and it may be facilitated by uterine contractions that would not be occurring in the ordinary course during perineal dusting. In addition, menstrual fluid contains blood and endometrial cells, which is very different from talc particles.

Dr. Zelikoff – Dr. Zelikoff goes even further down the path of speculation, opining that ultrafine particles can migrate from the respiratory system to the systemic circulation.²¹ As shown below, the studies she relied on did not use talc, explored the effects of particles on rats, rabbits or other animals with dissimilar anatomy to humans, involved dissimilar exposure conditions, including high doses and direction installation or *injection* of the particulate into the body, and did not study particle migration to the reproductive system or the translocation theory

¹⁶ Terry et al., *Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls*. Cancer Prev Res (Phila). (2013) 6(8):811-21.

¹⁷ Cramer et al., *Genital talc exposure and risk of ovarian cancer*. (1999) 81(3) Int J Cancer. 351.

¹⁸ Mills et al., *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*. (2004) 112 Int’l J. Cancer 458.

¹⁹ Tiourin et al., *Tubal Ligation Induces Quiescence in the Epithelia of the Fallopian Tube Fimbria*. Reprod Sci. (2015) 22(10):1262-71.

²⁰ Wolf Rep. at 10.

²¹ Zelikoff Rep. at 14-17.

pertaining to the reproductive system.

- Werebe, et al.'s study, *Systemic distribution of talc after intrapleural administration in rats*,²² injected high doses of talc slurry directly into the pleural cavities of rats, and found talc particles throughout organs, including the chest wall, lungs, heart, brain, spleen and kidneys, of rats 24-48 hours after injection. This study has limited applicability to the question of talc in humans because it was performed on rats, involved direct application into the pleural cavity, and the authors did not look at whether talc was found in the reproductive system.
- Driscoll et al., *Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells*,²³ explored the intratracheal installation in rats of quartz, carbon black and titanium dioxide at levels eliciting a neutrophilic inflammatory response found to increase mutation of cells in lungs. This study involved rats, did not involve talc, used direct installation of particulate into the body (not perineal application), involved dissimilar dose exposure conditions, did not look at the reproductive system and did not explore any translocation theory.
- In Ferrer et al.'s article, *Influence of particle size on extrapleural talc dissemination after talc slurry pleurodesis*,²⁴ high doses of two different sizes of talc were injected into the pleural cavities of 20 rabbits. The authors observed greater systemic talc particle deposition of smaller sized talc particles in the lungs, chest wall, diaphragm, mediastinal pleura, heart, liver, spleen and right kidney 24 hours and 7 days after exposure. The authors also noted greater inflammation with talc particles of a smaller size. Importantly, the trends noted were not consistent across rabbits or locations. For example, after 24 hours, no talc was found deposited in the liver for any rabbits, but after 7 days, only 3 of the 5 rabbits demonstrated talc in the liver. And although 1 out of 5 rabbits had talc depositions in the kidney after 24 hours, no rabbits had talc in the kidney after 7 days. These inconsistencies render the analysis of this article impossible to interpret. Moreover, the relevancy of this study is also limited as the study involved rabbits, used direct injections, involved dissimilar dose exposure conditions, did not look at the reproductive system or how the translocation theory applies to the reproductive system and utilized small sample sizes. There was no direct evaluation of reproductive tissues to determine whether any talc particles were deposited in them. It should be noted that in pleurodesis in human patients, there is no reported increase in ovarian cancer nor the presence of talc in the reproductive organs.²⁵

²² Werebe et al., *Systemic distribution of talc after intrapleural administration in rats*. Chest. (1999) 115(1):190-3.

²³ Driscoll et al., *Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells*. Carcinogenesis. (1997) 18(2):423-30.

²⁴ Ferrer et al., *Influence of particle size on extrapleural talc dissemination after talc slurry pleurodesis*. Chest. (2002) 122(3):1018-27.

²⁵ Viskum K, et al. *Long term sequelae after talc pleurodesis for spontaneous pneumothorax*. Pneumologie. (1989) 43:105-6.

- Genofre et al., in a study entitled *Talc pleurodesis: evidence of systemic inflammatory response to small size talc particles*,²⁶ injected high doses of two different sizes of talc – small (1.6-7.3 μm , mean: 6.41 μm) or mixed (6.4-50.5 μm , mean: 25.4 μm) particles – in the pleural cavities of 30 rabbits. The authors observed acute systemic inflammatory response for both small and mixed talc injection groups, but “small particle talc produced a more pronounced pleural and systemic response and resulted in greater particle deposition in the organs than mixed talc.” The particles found in the organs were smaller than 5 μm , and a significantly larger number of talc particles were observed in both lungs, the liver and kidneys in the small particle talc group compared to the mixed talc group, whereas no significant difference was observed for the spleen. The authors stated that the data did not permit a conclusion as to whether systemic cellular response was due to flow of cells from “pleural cavity to the bloodstream or to a direct system cellular response to the presence of talc particles in the organs,” but they speculated that “intense pleural inflammation caused by talc promotes the loss of integrity of the pleural barrier, permitting the free flow of cytokines and talc particles between the two compartments.” The relevancy of this study is limited as the study involved rabbits, used direct injections, involved dissimilar dose exposure conditions and did not look at the reproductive system or how the translocation theory applies to the reproductive system.
- Hollinger, *Pulmonary toxicity of inhaled and intravenous talc*,²⁷ merely compiles a handful of studies purportedly showing that talc can be accidentally inhaled or injected as part of drug abuse and studies purportedly showing that talc particles trapped in the lungs can induce foreign body granulomas and pulmonary fibrosis. The article does not present any new findings or data and is limited because it does not address translocation of talc outside of the lungs and involves exposure conditions dissimilar to perineal talc application, including dose.
- Kreyling et al., *Ultrafine particle-lung interaction: Does size matter?*,²⁸ reviewed existing literature on inhalation of insoluble ultrafine particles inhaled and systemic translocation. No talc studies were considered by the authors and the analysis was limited to inhalation and respiratory system studies, with no consideration of translocation to the reproductive system.
- Nakane’s *Translocation of particles deposited in the respiratory system: a systematic review and statistical analysis*²⁹ is a systematic review and statistical analysis of previous reports on particle translocation from the respiratory system. Although the article found that particle size was a strong factor for translocation, the authors did not consider any

²⁶ Genofre et al., *Talc pleurodesis: evidence of systemic inflammatory response to small size talc particles*. *Respir Med.* (2009) 103(1):91-7.

²⁷ Hollinger, *Pulmonary toxicity of inhaled and intravenous talc*. *Toxicol Lett.* (1990) 52(2):121-7.

²⁸ Kreyling, Semmler-Behnke & Möller, *Ultrafine particle-lung interaction: Does size matter?* *J Aerosol Med.* (2006) 19(1):74-83.

²⁹ Nakane, *Translocation of particles deposited in the respiratory system: a systematic review and statistical analysis*. *Environ Health Prev Med.* (2012) 17(4):263-74.

talc studies and limited translocation to the respiratory system, with no consideration of translocation to the reproductive system. The authors also noted that their analysis was hindered by a deficiency of information, information bias, publication bias and non-consideration of differences in structures and fabrications of different particles. The relevance of this review to the role of talc in the development of ovarian cancer remains very unclear.

- The Peters et al. study, entitled *Translocation and potential neurological effects of fine and ultrafine particles a critical update*,³⁰ addresses particulate air pollution and its association with cardiovascular and neurodegenerative effects and summarizes evidence pertaining to mechanisms involved in the translocation of particles from the lung to other organs. The authors state that their work demonstrates particles can be translocated to other organs by circulating blood, although they caution that “it remains to be shown by which mechanisms ultrafine particles penetrate cellular membranes by non-specific means.” The authors also note that some studies did not demonstrate translocation to the lung from other organs. The relevancy of this study is further limited as the article did not include any talc studies and was limited to translocation from the respiratory system with no discussion of translocation to the reproductive system.
- In Rossi’s et al.’s *Acute inflammatory response secondary to intrapleural administration of two types of talc*,³¹ 100 rabbits received intrapleural injections of large quantities of two different sizes of talc. The authors reported increased pulmonary and inflammatory response from talc particles, with greatest effects seen from the smaller talc particles. However, the authors observed no difference in the number of talc particles in the lungs between the control and test groups and did not observe an increased inflammatory response in talc-injected subjects with all parameters. Additionally, the relevancy of this study is also limited as the study involved rabbits, used direct intrapleural injections, involved dissimilar dose exposure conditions, did not look at the reproductive system or how the translocation theory applies to the reproductive system and utilized small sample sizes.

Dr. Levy – Dr. Levy appears to posit that talc could produce an inflammatory “environment” that could contribute to the development of ovarian cancer even without reaching the ovaries through “secondary effects” from unidentified “neighboring or surrounding tissues.”³² But as Dr. Levy acknowledged, this theory is “uninvestigated,” and he is “not aware of any studies that have made that delineation of talc exposure to neighboring or surrounding organs.”³³ Neither am I, and Dr. Levy’s unsupported musings certainly do not provide scientific evidence that talc can migrate sufficiently far from the perineum to produce an effect on the

³⁰ Peters et al., *Translocation and potential neurological effects of fine and ultrafine particles a critical update*. Part Fibre Toxicol. (2006) 8;3:13.

³¹ Rossi et al., *Acute inflammatory response secondary to intrapleural administration of two types of talc*. Eur Respir J. (2010) 35(2):396-401.

³² Levy Dep. 165:2-166:12.

³³ Levy Dep. 165:10-16.

ovaries, either directly or by “secondary effects.”

III. STUDIES ON THE BIOLOGIC EFFECTS OF TALC ON OVARIES

Studies on the biologic effects of talc on the ovarian epithelium have been limited in number and in general are of poor quality. In fact, the best study to date on the *in vivo* effects of talc on the rat ovary is Hamilton et al., *Effects of Talc on the Rat Ovary*,³⁴ which undermines plaintiffs’ theories because exposure to high amounts of talc did not result in the development of ovarian cancer. Several of plaintiffs’ experts cite Hamilton for the proposition that talc exposure leads to “adverse effects” on rat ovaries (e.g., McTiernan Rep. at 62; Wolf Rep. at 12; Plunkett Rep. at 26, 39), but in so doing, they miss the main point of the study, which is that none of the rats developed ovarian cancer.

Below, I address the studies relied on by plaintiffs’ experts, the Hamilton study and plaintiffs’ various theories regarding “inflammation.”

A. Buz’Zard

Several of plaintiffs’ experts rely on a study by Buz’Zard et al. entitled: *Pycnogenol reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures*,³⁵ which reported that talc increases the cellular proliferation of normal ovarian epithelial cells and a granulosa cell line, induces cellular neoplastic transformation and generates reactive oxygen species in cell culture.³⁶ To the extent these experts rely on this study to support the conclusion that talc exposure can cause ovarian cancer, that is wrong for a number of reasons.

First, the authors utilized a granulosa cell line, which is irrelevant to epithelial ovarian cancer. In addition, the “normal” ovarian cells tested were not normal; rather, they were immortalized. Although the method is not described in this paper, it is likely they were immortalized by SV40 (large and small T), which means they can grow in 3D cultures and by definition are not normal. Normal cells are critical to these types of studies because they will determine the true effects of talc.

³⁴ Hamilton et al., *Effects of Talc on the Rat Ovary*. Br J Exp Pathol. (1984) 65(1):101-6.

³⁵ Buz’Zard & Lau, *Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures*. Phytother Res. (2007) 21(6):579-86.

³⁶ For example, Dr. Siemiatycki cites this study for the proposition that “[a]lternative plausible mechanisms of carcinogenicity include talc induced oxidative stress.” (Siemiatycki Rep. at 65.) Similarly, Carson portrays this study as showing that “[t]alcum powder caused proliferation of human ovarian cells in culture, and causes these cells to express reactive oxygen species.” (Carson Rep. at 5.) And Kane claims that this study is evidence “that talc causes neoplastic transformation in ovarian cells.” (Kane Rep. at 36.) Several other experts also rely on this study for similar propositions. (Singh (page 19), Plunkett (page 42), Zelikoff (page 25), Wolf (page 12), Blair Smith (page 17), Clarke-Pearson (page 4), McTiernan (page 60) and Levy (page 14).)

Second, the proliferation assays are difficult to interpret due to the fact that they are viability assays, which only indirectly measure cell number. It is critical that they directly count cells to ensure cellular proliferation has increased.

Third, the effects of talc are minimal, time-dependent and divergent depending upon dose. For example, an increase in the viability assay seen at 24 hours disappears at 72 hours, a result that is difficult to rationalize. Are the control cells growing faster at 72 hours or are the treated cells starting to die? Certainly, the talc remains in the culture fluid. This seems very hard to interpret along with the opposite effects depending upon the talc concentration. Specifically, high concentrations result in inhibition on control cells, while lower concentrations are reported to be stimulatory – an anomalous result. There is no data to explain any of these results.

Fourth, the only measure of cellular transformation is soft agarose growth. It is well known that this assay can provide misleading results in that many human tumors do not grow in these conditions and non-transformed cells can. In fact, the OSE2a cells used in these experiments are likely an example of non-transformed cells, which grow in soft agarose. In figure 2 of the paper, the OSE2a cells demonstrate low but nevertheless cloning ability. Thus, these cells are already able to grow in 3D without any talc exposure – meaning that their growth does not signify malignancy. A much more accurate measure of neoplastic transformation is tumor formation in immunodeficient mice. This is a generally accepted and standard assay for determining whether cells are malignant. But it was not done in this study. Thus, the measure of increased 3D growth after talc treatment is problematic in that the untreated cells are already cloning, and more importantly, this is not a measure of transformation.

Fifth, the paper reports that “*talc caused an initial dose-dependent decrease in ROS [Reactive Oxygen Species] generation which increased with time in OSE2a cells.*”³⁷ This is not the case. All doses and time points except one (50ug/ml at 120 hours) remained below the control levels. Talc does not increase ROS production in this system; to the contrary, the general effect of talc was to *decrease* ROS relative to controls, and it was this effect that changed over time.

Sixth, there are no controls in this study, such as non-talc particles of approximately the same size (glass beads). This is critical, as it would help determine whether any effects of exposure were attributable to talc specifically, or rather the physical size and shape of the particles (in which case any effects of exposure would not be specific to talc).

Seventh, the effects of pycnogenol are irrelevant to this litigation. This is an experimental agent, which has no approved medical indications. Its effects on ovarian cancer cells are irrelevant to questions about talc.

In short, the Buz’Zard study does not provide a reliable basis for plaintiffs’ experts’ inflammation hypothesis because, among other things, it used an irrelevant cell line, the effects of talc treatment are conflicting and difficult to interpret and no controls were used. Of further note, the article was published in 2007, and yet even today there is no general acceptance of the notion that talc use fosters an inflammatory process that leads to ovarian cancer.

³⁷ Buz’Zard & Lau (2007).

B. Shukla

Another study cited by a number of plaintiffs' experts is *Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity* by Shukla et al.³⁸ For example, Dr. Plunkett cites this study to argue that the available *in vitro* and animal study data show that there is a dose-response relationship for talc toxicity.³⁹ This study does not support plaintiffs' experts' conclusions because it addresses gene expression – which cannot by itself tell us anything about the ostensible carcinogenicity of talc – and focuses largely on mesothelial cells and asbestos and, to the limited extent it addressed talc and ovarian cells, it showed no effect on gene expression.

The Shukla study reports the effects of low or high concentrations of crocidolite asbestos, nonfibrous talc, fine titanium dioxide or glass beads on immortalized mesothelial cells and human ovarian epithelial cells. Its primary endpoint was on gene expression levels. While gene expression is a molecularly interesting endpoint, its precise biologic effect and impact can be quite complex and difficult to predict. Many physical and biochemical stimuli can alter gene expression patterns without an obvious resulting biologic change. Distinguishing a real effect from background regulatory noise can be very difficult. The changes seen in this paper are relatively small in amplitude and in number. Validation by both real time Polymerase Chain Reaction and protein evaluation, along with careful biologic experiments, would be required to conclude that the changes are relevant.

This study also attempted to control for the presence of particles by using glass beads and titanium. Unfortunately, as shown in Table 1, there is considerable variation in size and surface area. Figure 2 shows little effect of talc on IOSE cell viability (in contrast to the report by Buz'Zard). The vast majority of this paper focuses on gene expression changes in primarily mesothelial cells after exposure to these agents (figure 3, 4, 5, 6 and table 2, 3). As such (for the reasons just explained), the relevance of these experiments and the results is questionable. The only results directly relevant to ovarian cancer are shown in Table 4. A small number of genes in IOSE cells (2 at 8 hours with high concentrations) showed increased expression with asbestos with only 15 genes at 24 hours. More importantly, nonfibrous talc, titanium and glass beads showed no effect on IOSE cells.

C. Hamilton

In contrast to the above studies, there are more direct examinations of the effects of talc in *in vivo* models that undermine plaintiffs' experts' arguments. These types of experiments utilize rodent models, which can provide important detailed data on the relevance of talc exposure to the development of ovarian cancer. The first study was by Hamilton et al. entitled *Effects of talc on the rat ovary*,⁴⁰ which exposed rat ovaries to high concentrations of talc by

³⁸ Shukla et al., *Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity*. Am J Respir Cell Mol Biol. (July 2009) 41(1):114-23.

³⁹ Plunkett Rep. at 50. Dr. Clarke-Pearson opines that this study demonstrated *in vitro* that crocidolite asbestos and non-fibrous talc caused expression of genes in ovarian epithelial cells producing inflammatory cytokines. Clarke-Pearson Rep. at 4.

⁴⁰ Hamilton et al. (1984).

direct intrabursal injections. The animals were followed for up to 18 months and then had their tissues carefully examined after being sacrificed. While the animals showed cystic changes to their ovaries, there were no cases of ovarian cancer. Microscopic evaluation showed mostly unaffected surface epithelial cells, and, in four cases, papillary changes. These structures were composed of normal looking cells without any atypia. In addition, and perhaps more importantly, in five cases there were cortical foreign-body granulomas without any evidence of inflammatory infiltration found. There was no correlation between these granulomas and the papillary structures. These benign findings led the authors to consider alternative hypotheses, such as elevated hormone exposure.

The second study utilized an inhalation model for talc effects by exposing rats and mice to high concentrations of aerosolized talc.⁴¹ This project, conducted by the National Toxicology Program, demonstrated that while there were lung toxicities induced by talc, there was a much more modest tumor effect. The few carcinomas in female rats could only be found in those with prolonged exposure to high levels of talc, and there was no greater incidence of malignant ovarian tumors in the exposed group.

D. Inflammation Theory

Inflammation has frequently been cited by plaintiffs' experts as the mechanism by which talc could increase the risk for ovarian cancer. In supposed support of this theory, they cite epidemiologic studies relating to the association of other inflammatory states with the increased risk of ovarian cancer and the use of NSAIDs and/or aspirin with an inverse risk of ovarian cancer. However, a close look at this data demonstrates that these studies do not support a relationship between inflammation induced by talc and the development of ovarian cancer.

Studies regarding inflammatory conditions and the risk of ovarian cancer have considered pelvic inflammatory disease (PID) and endometriosis.

- 1.) PID is an infection of the tubes and ovaries usually from a sexually transmitted disease. It is usually acute in nature but can become chronic. There have been multiple studies of the incidence of ovarian cancer in women with PID with inconsistent results.⁴² A more recent larger nationwide cohort study in Taiwan demonstrated an association of PID with ovarian cancer.⁴³ This study had only a three-year follow-up, and as such, many of the cancers may have been present at the

⁴¹ National Toxicology Program, *Toxicology and Carcinogenesis Studies of Talc (CAS NO. 14807-96-6) in F344/N Rats and B6C3F₁ Mice (Inhalation Studies)*, Technical Report No. 421 (Sept. 1993).

⁴² Rasmussen et al., *Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies*. Am J Epidemiol. (2017) 185(1): 8–20; Shen et al., *Risk of uterine, ovarian and breast cancer following pelvic inflammatory disease: a nationwide population-based retrospective cohort study*. BMC Cancer. (2016) 16(1):839; Zhou et al., *Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis*. Cancer Causes Control. (2017) 28(5):415-428.

⁴³ Lin et al., *Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study*. Lancet Oncol. (2011) 12(9):900-4.

same time as PID. This is a serious flaw because it begs the question: Did PID increase the risk of ovarian cancer or did the cancer increase the risk of PID?

- 2.) Endometriosis is commonly cited as another inflammatory condition that is associated with ovarian cancer. This is also highly misleading, for several reasons. First, endometriosis is not associated with an increased risk of high grade serous ovarian cancer (HGSOC). HGSOC is the most common histology of ovarian cancer, has the highest mortality rate, and has been the primary focus of several of plaintiffs' experts. Endometriosis is associated with endometrioid and clear cell ovarian cancer histologies. Second, although there is frequently tissue reaction around endometriosis, including the infiltration of components of the immune system, endometriosis is really an ectopic displacement of endometrial tissue. This means that the endometrium is located outside of the uterus and as the endometrial tissue cycles, just like "normal" endometrial tissue, it will bleed and slough. This process obviously will lead to some local tissue reaction, and in some cases, fibrosis. There are no data that the tissue reaction is in fact the contributing factor versus the displaced endometrial cells. There are other well-known examples of displaced epithelial tissue increasing the risk of developing cancer. A good example is Barrett's esophagus, where gastric mucosa extends up into the distal esophagus where it does not usually reside, but in that position increases the risk of esophageal cancer.

The association between use of NSAIDs and/or aspirin and a decreased risk of ovarian cancer has also been cited as evidence for an inflammatory basis for the origin of ovarian cancer. But the supporting data do not make a persuasive argument. A meta-analysis of multiple epidemiologic studies examining the association of NSAIDs/aspirin use with ovarian cancer risk did not show any preventive effect.⁴⁴ This is an important analysis, as it is a very large study and includes all relevant studies up to 2012, concluding that there is no statistically significant association between NSAID use and the prevention of ovarian cancer. After extensive sorting, 21 studies met the appropriate criteria, and of these, 14 were case-control studies and 7 were cohort studies. The meta-analysis of these studies with regard to aspirin and NSAIDs showed no protective effects of these agents against the development of ovarian cancer. Even the subset analysis fails to show any meaningful association between the use of these drugs and a decreased risk of developing ovarian cancer. The authors conclude that, "[b]ased on this meta-analysis, the association between aspirin and non-aspirin NSAID use and ovarian cancer risk is weak."⁴⁵

Some studies have evaluated markers of inflammation for possible correlations with ovarian cancer and these studies have been inconclusive or, if anything, have suggested that inflammation is not linked to ovarian cancer carcinogenesis. In one study by Trabert and others,

⁴⁴ Baandrup et al., *Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies*, Acta Obstet Gynecol Scand. (2013) 92(3):245-55; Bonovas et al., *Do Nonsteroidal Anti-Inflammatory Drugs Affect the Risk of Developing Ovarian Cancer? A Meta-Analysis*, Brit. J. Clinical Pharmacology (2005) 60(2): 194-203; Ni et al., *Meta-Analysis on the Association Between Non-Steroidal Anti-Inflammatory Drug Use and Ovarian Cancer*, Brit. J. Clinical Pharmacology (2012) 75(1) 26-35.

⁴⁵ *Id.*

the authors investigated 46 inflammatory serum markers for possible association with ovarian cancer.⁴⁶ Of the 46 markers studied, only two – C-reactive protein (CrP) and Interleukin (IL)-1 α – were associated with the risk of developing ovarian cancer. The implications of this finding are unclear. As the authors acknowledged, because the markers were present in serum, the measurements can only report systemic levels, and thus “may not reflect levels in local sites of inflammation relevant to ovarian carcinogenesis, which may include the fallopian tubes, ovary, or endometriotic lesions.” As a result, the implications of the findings are unclear and do not substantiate a link between local inflammation and ovarian cancer.

Another study identified three cohorts of women, including: (1) 60 women who had undergone risk-reducing removal of their ovaries and fallopian tubes because of hereditary risks for ovarian cancer; (2) 18 women who had undergone surgery for ovarian cancer without any known hereditary risks for the disease; and (3) 23 women (control group) who had undergone surgery to remove their fallopian tubes with benign diagnoses. The authors examined histological slides for markers of inflammation, including a lower ratio of ciliated cells, higher numbers of lymphocytes, and longer fimbria length (the fimbriae are tissues between the fallopian tubes and ovaries). Although the authors found increased inflammation between the cancer group and the control group, the trend was not statistically significant. The authors also noted that age could have been a confounder because the mean age of women with cancer was four years higher than the women in the control group. The authors concluded that “no significant correlation was made between serous carcinoma and histological signs of inflammation” and that more research is necessary “to further evaluate the role of inflammation in carcinogenesis in the fallopian tube.”⁴⁷

IV. DR. SAED’S PLAINTIFF-FUNDED RESEARCH

One of plaintiffs’ experts, Dr. Ghassan Saed, opines that his work has established a plausible biological mechanism by which ovarian cells exposed to talc could develop cancer, an opinion he sets forth both in a report prepared for this litigation and in an in-press manuscript.

As discussed at length below, Dr. Saed’s research suffers from a number of severe methodological flaws, rendering it at times uninterpretable and certainly unreliable. None of the findings he reports has been shown to cause cancer in general, much less ovarian cancer. Dr. Saed also makes some of the same unsubstantiated assumptions as plaintiffs’ other experts about the significance of alterations in gene expression or the effects of inflammation or levels of ROS. Moreover, he has not made any effort to replicate his *in vitro* findings *in vivo*, as noted by one reviewer for *Gynecologic Oncology*, which rejected his manuscript.⁴⁸ Because cells in living tissue react differently than cells in a laboratory, it is widely accepted that, while *in vitro* studies

⁴⁶ Trabert et al., *Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial*. *Gyn. Onc.* (2014) 135:297-304.

⁴⁷ Malmberg et al., *Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development*. *Virchows Arch.* (2016) 468(6):707-13.

⁴⁸ Saed II Dep. Ex. 35 (Gynecologic Oncology Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision).

provide a valuable starting point, no conclusions about human health can be drawn from them. As another *Gynecologic Oncology* reviewer explained, “the present data are insufficient to support the claim that talcum is central to the development of ovarian cancer.”⁴⁹

Due to the flaws in Dr. Saed’s methodology, his work cannot support even his more modest conclusions. His opinion is subject to many of the same problems identified above in other work. For example, Dr. Saed presumes that perineal talc use would result in exposure of ovarian tissue to talc through migration, but such migration has not been established. In addition, Dr. Saed’s methodology is flawed in a number of different ways. Most importantly, he did not use rigorous methods in his research, and his report is filled with speculation and guessing that he mischaracterizes as scientific knowledge.

A. Dr. Saed’s Report

Dr. Saed’s report is filled with generalities regarding ovarian cancer that are not supported by any citations and reflect a superficial understanding of the disease. For example:

- He refers to “malignant overgrowth versus a benign overgrowth, specifically postoperative adhesions.”⁵⁰ But he does not explain what postoperative adhesions have to do with ovarian cancer development, and from a scientific standpoint, there is no generally accepted connection.
- On pages 5-6, he states that “two enzymes, MPO and iNOS, work together to inhibit apoptosis, a hallmark of ovarian cancer.” There are no references for this statement. I know of no scientific basis for stating that these two enzymes inhibit apoptosis or that apoptosis is critical for the development or progress of ovarian cancer. Notably, there is no reference supporting that apoptosis is a “hallmark” of ovarian cancer.
- There is an extensive discussion on page 7 concerning CA-125 and HE4 as serum biomarkers for ovarian cancer. It is completely unclear what this has to do with the role of talc in ovarian cancer development. The fact that CA-125 can be elevated in cases of ovarian cancer does not mean it can contribute to cancer causation. To take a simple example, a fever may be a “biomarker” for a bacterial or viral infection, but the fever obviously does not contribute to causing the infection. While HE4 has recently been proposed as a possible ovarian cancer biomarker as well in certain studies, the suggestion that it can contribute to cancer causation is even more speculative.
- On page 17, Dr. Saed makes the statement: “Consistent with these findings, recent studies from my laboratory have shown that talc enhances cell proliferation and induces an inhibition in apoptosis in EOC cells, but more importantly in normal cells, suggesting talc is a stimulus to the development of the oncogenic

⁴⁹ *Id.*

⁵⁰ Saed Rep. at 2.

phenotype.” As discussed below, he includes no reference for this statement. But even if it is true, cell proliferation and inhibited apoptosis can also occur in healthy and non-malignant cells and therefore cannot be broadly characterized as an “oncogenic phenotype.” I note with concern that Dr. Saed does not seem to appreciate this very basic, well-established fact. At his deposition, Dr. Saed expressed belief that his tests showed development of neoplastic cells because he reported finding “[p]roliferation,” which he claimed was “an indirect measure of the beginning of a transformation.”⁵¹ This is not so. One might well expect to see accelerated cell proliferation where a neoplastic transformation has occurred, but accelerated cell proliferation itself does not serve to identify the existence of a neoplastic transformation.⁵² Many normal tissues proliferate, including the endometrium, cervical epithelium, colonic epithelium and even skin.

- On page 5, he discusses the GSH/GSSG complex and its stimulation of the activity of GS-X-MRP1 efflux pump and its relation to the development of resistance to chemotherapeutic drugs. This is obviously irrelevant to the development of ovarian cancer, and GS-X-MRP1 efflux pump activity has no clinical significance in the treatment of ovarian cancer either.

Dr. Saed’s experiments do not reflect an in-depth understanding of ovarian cancer and are methodologically flawed in a number of ways. Most notably:

- Dr. Saed’s cell line work involves cancer cell lines, which are not high grade serous ovarian cancer (HGSOC) cell lines. TOV112D (endometrioid), SKOV-3 (endometrioid or clear cell), and A2780 are not HGSOC cell lines, and as such have no relevance to HGSOC, the most common subtype of ovarian cancer and a key focus of the epidemiology and plaintiffs’ expert. Therefore, these cell line models and the data derived from them do not support the role of talc in the development of ovarian cancer. This is a serious flaw in Dr. Saed’s work, and it reflects a certain lack of understanding of the state of the science in ovarian cancer research. Similarly, only one of his three normal cell lines, FT33, was from fallopian cells – the relevant cell type given that most ovarian cancer is now known to start in the fallopian tubes. And this cell line was immortalized, meaning that, by definition, the cells were not normal and the impact of talc on normal fallopian cells remains untested.
- Most of the experiments are conducted using doses (5-100 ug/ml) applied directly to ovarian cells that are inconsistent with exposure of ovarian tissue to talc that women might experience dusting their perineum with powder (indeed, there likely is no such exposure, as discussed above). These are enormous doses and there is no data to support that the doses used in these experiments are what the female genital tract would be exposed to from the dusting of the perineum, even

⁵¹ Saed II Dep. 464:2-11.

⁵² Chaffer & Weinberg, *How does multistep tumorigenesis really proceed?* Cancer Discov. (2015) 5(1):22-4.

assuming that some talc could migrate up to the fallopian tubes or ovaries. It is certainly not consistent with the reported detection of talc particles in ovarian cancers, which are exceedingly small in numbers.

There is considerable discussion about SNPs in the document. It is exceedingly difficult to follow and understand. There are multiple references to mutations in SNPs, but it is unclear what the author is referring to. SNPs are inherited and exist at birth and therefore each person has a unique pattern of SNPs. It might be that Dr. Saed is referring to this fact, or he could be hypothesizing somatic mutations within the tumor or even the fertilized egg (or perhaps something else entirely). If Dr. Saed is claiming that talc treatment of the cells caused the development of specific SNPs that did not previously exist through mutation, he has provided no evidence of that hypothesized effect or how it would work. The imprecision in these statements is important, as it reflects shortfalls in the thought process and expertise that went into the report.

There is also an extensive discussion about the impact of SNPs on protein function and their association with ovarian cancer. Dr. Saed makes the argument that many of these SNPs result in amino acid changes and the resultant proteins have altered functions. This results in changes in oxidants and antioxidants, which, it is argued, affects ovarian cancer risk and development. The data presented are very poor and confusing. None of the studies on which Dr. Saed relies show any relationship between the SNPs he identified and increased risk of ovarian cancer. Most of what is referenced are general reviews or papers discussing SNPs in “oxidative DNA repair genes and redox genes with human cancer susceptibility.”⁵³ The specific relevance of this for ovarian cancer is unclear. Further SNP data is extracted from ovarian cancer Genome Wide Association Studies (GWAS) studies, and by and large they demonstrate small but statistically significant associations of specific SNPs with the risk for ovarian cancer. These SNPs have had no clinical impact on the management of ovarian cancer patients or cancer prevention/screening. In addition, the mechanism(s) by which these SNPs affect cell behavior remains completely unknown; in particular, it is unknown whether any of these SNPs affect the function of the proteins synthesized from the affected DNA, much less whether the SNPs can ultimately affect the redox state of cells.

Dr. Saed also utilizes a mixture of other investigators’ work in systems other than ovarian cancer, SNP data in ovarian cancer patients and his own work using ovarian cancer cell lines (most of which are not HGSOC) to support the contention that these genes and their SNPs play a role in the development of ovarian cancer. The former work, which, as mentioned, does not involve ovarian or fallopian tissue, is irrelevant to ovarian cancer, as complexity of tissues and their biochemistry can make functional results completely different from one human tissue to another.

Dr. Saed’s interpretation of his own work is even more problematic. With respect to the ovarian cancer SNP data, he refers to the presence of a particular SNP with patient survival. But he does not explain what a prognostic marker has to do with risk markers. Is he arguing they are the same? As discussed in the context of proteins, prognostic markers may be associated with ovarian cancer or with ovarian cancer survival without playing a role in causation. On the bottom

⁵³ Saed Rep. at 7.

of page 8, Dr. Saed lists many SNPs associated with the risk of ovarian cancer (*notably, none of which was found in his experiment*) and admits that they are “near” genes, which are not associated with redox/oxidative stress. In fact, this is correct; the SNPs are just genomic markers and may identify neighboring genes, which are the actual ones that ascribe the risk. The genes in which the SNP mutation actually occurred are likely to have no role in oxidative stress or redox.

Dr. Saed’s research is also unreliable because it is impossible to understand exactly what he did. There is little or no primary data, and what is described is insufficient. In short, he offers a host of conclusions about the results of his study, but no data that would allow those conclusions to be evaluated or replicated.

- On page 18, it is stated that “treatment of normal or ovarian cancer cells with talc resulted in a significant increase in MPO and iNOS.” There is no reference or data presented. Although I understand that Dr. Saed has produced lab books that are supposed to contain the underlying data, those data have proven unreliable in several respects. Specifically, at his deposition, Dr. Saed repeatedly admitted to what he called “typos” or errors concerning fundamental issues of dose, statistical significance and time of treatment.⁵⁴ He similarly acknowledged errors that he said he “can’t explain” in calculations contained within his lab books – the raw data on which his report and opinions are based.⁵⁵ The pervasiveness of these errors virtually ensures that there are other errors pertaining to critical points that reviewers of Dr. Saed’s work are in no position to uncover, calling all of his work and conclusions into even more doubt and rendering them scientifically unreliable.
- Dr. Saed uses cell lines (TOV112D, SKOV-3 and A2780) in his reported experiments, which do not reflect the epidemiologic data relating talc to the risk of ovarian cancer, and more importantly, the SNP data. As discussed above, none of his cell lines were HGSOC cell lines, and both the epidemiology and the SNP data studied primarily HGSOC cases.
- Dr. Saed also states that, “[c]onsistent with this finding, it has previously been reported that acquisition of chemoresistance by ovarian cancer cells is associated with a switch from the *GPXI* SNP genotype to the normal *GPXI* genotype.” Dr. Saed does not opine that talc makes existing ovarian cancer more difficult to treat, but rather that it causes ovarian cancer to develop in the first place. What does chemoresistance have to do with ovarian cancer development?
- Additionally, Dr. Saed reports: “our results showed that talc treatment was associated with a genotype switch from common C/C genotype in *NOS2* in untreated cells to T/T, the SNP genotype, in talc treated cells, except in A2780 and TOV112D.”⁵⁶ What is a genotypic switch? Is he reporting a direct mutation in

⁵⁴ Saed II Dep. 403:3-407:11, 416:9-417:7, 457:21-458:25, 542:3-15.

⁵⁵ *Id.* 450:24-453:24.

⁵⁶ Saed Rep. at 19.

the DNA? There is no suggestion in the literature that talc interacts with DNA and no data in his report or lab books providing an explanation of how that would be possible.

- Dr. Saed argues in his report that exposure to chemotherapy alters SNP profiles and this is important for the development of resistance. As mentioned above, Dr. Saed purports to offer an opinion about the development of ovarian cancer, not about its susceptibility to treatment. It is entirely unclear what chemoresistant SNP profiles have to do with talc and the development of ovarian cancer. Since 80% of ovarian cancers are drug-sensitive at diagnosis, if talc is associated with the development of resistance, then it is not associated with cancer development. Chemoresistant ovarian cancer develops after multiple recurrences and years of exposure to different drug regimens. What Dr. Saed describes is poorly presented, and more importantly makes little scientific sense.

B. Dr. Saed's Recent Manuscript

The manuscript entitled *Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer* by Fletcher et al.⁵⁷ (for which Dr. Saed is the corresponding author) describes a series of experiments attempting to demonstrate evidence for the role of talc in the development of ovarian cancer. Dr. Saed acknowledged at his deposition that this article was based on the same research as his expert report. Unsurprisingly, this manuscript has serious methodologic, experimental, and analysis flaws, including many of the same ones already identified. Specifically:

1. As was the case in his report, none of the cancer cell lines used are HGSOV cell lines. SKOV-3, A2780, and TOV112D are not of serous origin. It would be the same if the authors were using lung or colon cancer cell lines. These experiments are not relevant to the suggested role of talc in HGSOV. Similarly, just one of the normal cell lines is of fallopian origin, and one of them is not even derived from female reproductive tissue at all, but rather from macrophages.
2. Figure 1 shows a decrease in CAT mRNA expression only at high concentrations of talc. There is no evidence that this is the concentration of talc that women are exposed to when dusting their perineum. Talc does not show a decrease in SOD3 except at the 100ug/ml concentration. The control – a solution of pure DMSO – shows an 80% decrease by itself. The effect of the control suggests that to the extent Fletcher and Saed found that extremely high talc concentrations altered mRNA expression, the effect results from cell culture conditions, and not talc. Additionally, the mRNA levels were normalized to B-actin. Is this appropriate, as opposed to other house-keeping genes? Saed and Fletcher make no effort to justify their selection of B-actin, and the reported changes of gene expression levels could actually reflect different stabilities of the target genes versus

⁵⁷ Saed I Dep. Ex. 8 (Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM, *Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer* (2019) (unpublished manuscript)).

coupled with instable levels of the control B-actin. The manuscript does not address this possibility, which goes to the reliability of the reported results.

3. It is unclear whether figure 1 shows enzyme activity or protein levels. It is labeled ELISA (a test used to detect protein levels) and the text reports protein levels. Yet, the ordinate reflects some sort of enzyme activity. There are no methods describing the procedure used to generate the results, making them impossible to interpret.
4. The CA125 experiments showing increased CA125 levels under talc treatment have no relevance to the development of ovarian cancer. CA125 has no proven role in the development of ovarian cancer. As mentioned above, CA125 is sometimes used as an ovarian cancer biomarker, but that does not mean it can contribute to causing ovarian cancer. Moreover, CA125 gene regulation is controlled by many transcription factors.
5. Figure 5 utilizes the MTT assay as a measure for cellular proliferation. A direct cell count is necessary to ensure that the MTT result is correct. The MTT assay is a colorimetric assay that measures metabolic activity, which can be a proxy for a cell count. But MTT results could be misleading. As a matter of basic science, the MTT assay can only indirectly measure cell proliferation because what it detects is enzymatic activity, which is supposed to correlate to cell counts, but it has long been understood that this indirect measurement is subject to potential interference that can significantly impair its accuracy. In one study examining the accuracy of an MTT assay in control cells to which DMSO had been applied, for example, the true number of control cells was found to be “10-fold higher” than reported by the MTT assay.⁵⁸ Dr. Saed is apparently unaware of this problem.
6. Figure 6 reports decreased apoptosis in talc treated cells. There is no description of other mechanisms of cell death, including necrosis, etc. Because the study does not report other mechanisms of cell death, it is possible that overall cell death rates are the same in treated and non-treated cells. If the controls are, in fact, dying faster than the talc treated cells, then is there talc-induced proliferation?
7. The SNP data are very difficult to understand. Indeed, one of the reviewers for *Gynecologic Oncology* noted that “[t]he significance of SNP alterations should be further clarified.”⁵⁹ To the extent I can understand the data, they seem to suggest that treatment of the cultures (with decreased cellular apoptosis) somehow undergoes a specific DNA-based switch. It is not clear to me what a switch means. Do the authors mean a mutation of one of the alleles or selection of one of the alleles? The manuscript provides no data to explain why either of these things would happen. As mentioned, there are no data I am aware of – either in the literature or in Fletcher and Saed’s results – that a particle such as talc could specifically mutate DNA, and it is not apparent how it could. How does talc

⁵⁸ Plumb et al., *Effects of the pH dependence of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide-formazan absorption on chemosensitivity determined by a novel tetrazolium-based assay*. *Cancer Res.* (1989) 49:4435-4440.

⁵⁹ Saed II Dep. Ex. 35 (Gynecologic Oncology Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision).

enter the cell? How does it get into the nucleus? If it does not do those things, what is the mechanism by which it can alter DNA? A secondary process resulting for talc would not be expected to be specific for the DNA sequence. If selection, rather than mutation, is involved, then, again, what is the mechanism of selection? There are no data to address any of these questions, and quite frankly, the results as described are not plausible.

V. CONCLUSION

Much remains to be understood about ovarian carcinogenesis, and unfortunately, nothing plaintiffs' experts offer in their reports or depositions advances our understanding. Talc is not generally accepted as a cause of ovarian cancer. In fact, much of what plaintiffs' experts cite as supposed support for their conclusions on biological plausibility reflects work that attempted to – but did not – clarify a potential causal relationship between talc and ovarian cancer (and in many cases added significant support to the null hypothesis – i.e., that talc *does not* cause ovarian cancer). The little new science that plaintiffs' experts attempted to contribute to this inquiry – principally in the form of Dr. Saed's experiments – is deeply flawed at many levels as described in this report and, even ignoring these flaws, does not bring us any closer to establishing any hypothesized causal connection between talc use and ovarian cancer.

Materials Reviewed and Considered by Dr. Michael Birrer

1. Baandrup et al., Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand.* (2013) 92(3):245-55.
2. Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis.* *Eu J of Cancer Prev.* (2018) 27:248-257.
3. Bonovas et al., *Do Nonsteroidal Anti-Inflammatory Drugs Affect the Risk of Developing Ovarian Cancer? A Meta-Analysis.*, *Brit. J. Clinical Pharmacology* (2005) 60(2): 194-203.
4. Boorman et al., The Lack of an Ovarian Effect of Lifetime Talc Exposure in F344/N Rats and B6C3F1 Mice. *Regul Toxicol Pharmacol.* (1995) 21(2):242-3.
5. Booth et al., Risk factors for ovarian cancer: a case-control study. *Br J Cancer* (1989) 60:592-8.
6. Buz'Zard & Lau, Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytother Res.* (2007) 21(6):579-86.
7. Camargo et al., Occupational Exposure to Asbestos and Ovarian Cancer: A Meta-analysis. *Environ Health Perspect* (2011) 119(9):1211–1217.
8. Cancer Genome Atlas Research Network, Integrated genomic analyses of ovarian carcinoma. *Nature* (2011) 474(7353):609-15.
9. Cannistra, Cancer of the ovary. *N Engl J Med.* (2004) 351(24):2519-29.
10. Carr, Talc: Consumer Uses and Health Perspectives. *Reg Toxicol Pharmacol* (1995) 21:211-215.
11. Chaffer & Weinberg, How does multistep tumorigenesis really proceed? *Cancer Discov.* (2015) 5(1):22-4.
12. Chang & Risch, Perineal talc exposure and risk of ovarian carcinoma. *Cancer* (1997) 79:2396-401.
13. Chen et al., Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol* (1992) 21:23-9.
14. Cho & Shih, Ovarian cancer. *Annu Rev Pathol.* (2009) 4:287-313.
15. Cook et al., Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol* (1997) 145:459-65.
16. Cramer & Xu, Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol* (1995) 5:310-4.

17. Cramer et al., Genital talc exposure and risk of ovarian cancer. (1999) 81(3) Int J Cancer. 351.
18. Cramer et al., Ovarian cancer and talc: a case-control study. Cancer (1982) 50:372-6.
19. Cramer et al., Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. Obstet Gynecol. (2007) 110(2 Pt 2):498-501.
20. Cramer et al., The Association Between Talc Use and Ovarian Cancer: A Retrospective Case control study in two US States. Epidemiol. (2016) 27(3):334-346.
21. Cramer, Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol (1999) 94:160-1.
22. Crawford et al., Perineal powder use and risk of endometrial cancer in postmenopausal women. Cancer Causes Control 2012; 23:1673-80.
23. Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738)
24. Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738)
25. Driscoll et al., Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells. Carcinogenesis. (1997) 18(2):423-30.
26. DS Biotech, LLC Invoice to Beasley Allen, from Ghassan Saed, Ph.D., dated February 8, 2019 (Ex. 22 to the Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
27. Egli & Newton, The transport of carbon particles in the human female *reproductive tract*. Fertil Steril. (1961) 12:151-5.
28. Endo-Capron et al., Some in vivo and in vitro studies carried out with talc samples, NATO ASI Series G, 1990.
29. Expert Report of Anne McTiernan, M.D., Ph.D., Nov. 16, 2018 (MDL No. 2738)
30. Expert Report of Arch Carson, M.D., Ph.D., Nov. 16, 2018 (MDL No. 2738)
31. Expert Report of Daniel L. Clarke-Pearson, M.D., Nov. 16, 2018 (MDL No. 2738)
32. Expert Report of David A. Kessler, M.D., Nov. 16, 2018 (MDL No. 2738)
33. Expert Report of Ellen Blair Smith, M.D., Nov. 16, 2018 (MDL No. 2738)
34. Expert Report of Ghassan M. Saed, Ph.D., Nov. 16, 2018 (MDL No. 2738)
35. Expert Report of Jack Siemiatycki, M.Sc., Ph.D., Nov. 16, 2018 (MDL No. 2738)
36. Expert Report of Judith Wolf, M.D., Nov. 16, 2018 (MDL No. 2738)
37. Expert Report of Judith Zelikoff, Ph.D., Nov. 16, 2018 (MDL No. 2738)
38. Expert Report of Laura M. Plunkett, Ph.D., DABT, Nov. 16, 2018 (MDL No. 2738)

39. Expert Report of Patricia Moorman, M.S.P.H., Ph.D., Nov. 16, 2018 (MDL No. 2738)
40. Expert Report of Rebecca Smith-Bindman, M.D., Nov. 15, 2018 (MDL No. 2738)
41. Expert Report of Sarah E. Kane, M.D., Nov. 15, 2018 (MDL No. 2738)
42. Expert Report of Shawn Levy, Ph.D., Nov. 16, 2018 (MDL No. 2738)
43. Expert Report of Sonal Singh, M.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)
44. Faber et al., Oral contraceptive use and impact of cumulative intake of estrogen and progestin on risk of ovarian cancer. *Cancer Causes Control*. (2013) 24(12):2197-2206.
45. Ferrer et al., Influence of particle size on extrapleural talc dissemination after talc slurry pleurodesis. *Chest*. (2002) 122(3):1018-27.
46. Fiume et al., Safety Assessment of Talc as Used in Cosmetics. *Int J Toxicol*. (2015) 34(1 Suppl):66S-129S.
47. Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM, Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer (Oct. 10, 2018) (unpublished manuscript) (Ex. 38 to the Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
48. Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM, Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer (Jan. 3, 2019) (unpublished manuscript) (Exs. 7 & 8 to the Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
49. Food and Drug Administration, Letter from Musser SM to Epstein SS Re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP. Date stamped: April 1, 2014. April 1, 2014 FDA Denial of 1994 and 2008 Petitions.
50. Food and Drug Administration, Statement on Talc (2015).
51. Gates et al., Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype. *Am J Epidemiol* (2010) 171:45-53.
52. Gates et al., Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. (2008) 17:2436-44.
53. Genofre et al., Talc pleurodesis: evidence of systemic inflammatory response to small size talc particles. *Respir Med*. (2009) 103(1):91-7.
54. Gertig et al., Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. (2000) 92(3):249-52.
55. Ghassan Saed's PCR EOC SRI Notebook (Ex. 9 to the Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))

56. Ghassan Saed's Talc Study Lab Notebook – Preliminary Study (Ex. 23 to the Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
57. Godard et al., Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol* (1998) 179:403-10.
58. Gonzalez, Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiol.* (2016) 27(6):797-802.
59. Green et al., Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer* (1997) 71:948-51.
60. Gross et al., A Meta-Analytical Approach Examining the Potential Relationship Between Talc Exposure and Ovarian Cancer. *J Exp Anal Environ Epidemiol* (1995) 5:181-195.
61. Gynecologic Oncology Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision (Ex. 35 to the Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
62. Hamilton et al., Effects of Talc on the Rat Ovary. *Br J Exp Pathol.* (1984) 65(1):101-6.
63. Harlow & Hartge, A review of perineal talc exposure and risk of ovarian cancer. *Regul Toxicol Pharmacol* (1995) 21:254-60.
64. Harlow & Weiss, A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol* (1989) 130:390-4.
65. Harlow et al., Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* (1992) 80:19-26.
66. Hartge et al., Talc and ovarian cancer. *JAMA* (1983) 250:1844.
67. Heller et al., Asbestos exposure and ovarian fiber burden. *Am. J. Indus. Med.* (1996) 29:435-439.
68. Heller et al., Correlation of asbestos fiber burdens in fallopian tubes and ovarian tissue. *Gynecol.* (1999) 181:346-47.
69. Heller et al., Presence of asbestos in peritoneal malignant mesotheliomas in women. *Int. J. Gynecol. Cancer.* (1999) 9:452-455.
70. Heller et al., The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol.* (1996) 174(5):1507-10.
71. Henderson et al., Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonw.* (1971) 78(3):266-72.
72. Henderson et al., Talc in normal and malignant ovarian tissue. *Lancet.* (1979) 1(8114):499.

73. Hillegass et al., Utilization of Gene Profiling and Proteomics to Determine Mineral Pathogenicity in a Human Mesothelial Cell Line (LP9/TERT-1). *Journal of Toxicology and Environmental Health, Part A*, 73::423-436-2010
74. Hollinger, Pulmonary toxicity of inhaled and intravenous talc. *Toxicol Lett.* (1990) 52(2):121-7.
75. Houghton et al., Perineal Powder Use and Risk of Ovarian Cancer. *J Natl Cancer Inst* (2014) 106(90); dju208.
76. Huncharek et al., Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from 16 Observational Studies. *Anticancer Research* (2003) 23:1955-1960.
77. IARC, Arsenic Metals, Fibres, and Dusts, Vol 100 C.
78. IARC, Carbon Black, Titanium Dioxide, and Talc, Vol 93.
79. Jordan et al., Breastfeeding and risk of epithelial ovarian cancer. *Cancer Causes Control.* (2010) 21(1):109-116.
80. Jordan et al., Risk factors for benign serous and mucinous epithelial ovarian tumors. *Obstet Gynecol* (2007) 109:647-54.
81. Karageorgi et al., Perineal use of talcum powder and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev* (2010) 19:1269-1275.
82. Keskin et al., Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. *Arch Gynecol Obstet* (2009) 280:925-931.
83. Korsic et al., Talc pleurodesis improves survival of patients with malignant pleural effusions: case-control study *Wien Klin Wochenschr* DOI 10.1007/s00508-015-0716-8
84. Kotsopoulos et al., Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin. *Int J Cancer* (2013) 133:730-740.
85. Kreyling, Semmler-Behnke & Möller, Ultrafine particle-lung interaction: Does size matter? *J Aerosol Med.* (2006) 19(1):74-83.
86. Kunz et al., The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. *Adv Exp Med Biol.* (1997) 424:267-77.
87. Kurman & Shih, The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am. J. Surg. Pathol.* (2010). 34:433–443.
88. Lab Notebook, SAED000001(color)-SAED000097(color) (Ex. 1 to the Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738))
89. Lacey et al., Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer. *JAMA Network.* (2002) 288(3):334-341.

90. Langseth et al., Perineal use of talc and risk of ovarian cancer. *J Epidemiol Comm Health* (2008) 62(4):358-360.
91. Letter to Lawrence Layman, Editor, Reproductive Sciences, from Ghassan Saed, Ph.D., dated Jan. 2, 2019 (Ex. 40 to the Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))
92. Lin et al., Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol.* (2011) 12(9):900-4.
93. Litton Bionetics, Inc., Summary of Mutagenicity Screening Studies Host-Mediated Assay Cytogenetics Dominant Lethal Assay, December 9, 1974.
94. Malmberg et al., Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development. *Virchows Arch.* (2016) 468(6):707-13.
95. Merritt et al., Talcum powder chronic pelvic inflammation and NSAIDS in relation to risk. *Int J Cancer* (2007) 122:170-176.
96. Mills et al., Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California. (2004) 112 *Int'l J. Cancer* 458.
97. Muscat & Huncharek, Perineal talc use and ovarian cancer: a critical review. *Eur J Cancer Prev* (2008) 17:139-46.
98. Nakane, Translocation of particles deposited in the respiratory system: a systematic review and statistical analysis. *Environ Health Prev Med.* (2012) 17(4):263-74.
99. National Cancer Institute, Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ), Health Professional Version, <https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq>.
100. National Toxicology Program, Toxicology and Carcinogenesis Studies of Talc (CAS NO. 14807-96-6) in F344/N Raths and B6C3F1 Mice (Inhalation Studies), Technical Report No. 421 (Sept. 1993).
101. Neill et al., Use of talcum powder and endometrial cancer risk. *Cancer Causes Control* (2012) 23:513-519.
102. Ness et al., Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* (2000) 11:111-7.
103. Ness, Does talc exposure cause ovarian cancer? IGCS-0015 Ovarian Cancer. *Int J Gynecol Cancer* (2015) 25(Suppl 1):51.
104. Ni et al., Meta-Analysis on the Association Between Non-Steroidal Anti-Inflammatory Drug Use and Ovarian Cancer, *Brit. J. Clinical Pharmacology* (2012) 75(1) 26-35.
105. Penninkilampi & Eslick, Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology* (2018) 29(1):41-49.

106. Peres et al., Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies. *Int J Epidemiol* (2017) 1–13.
107. Peters et al., Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Part Fibre Toxicol.* (2006) 8;3:13.
108. Plumb et al., Effects of the pH dependence of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide-formazan absorption on chemosensitivity determined by a novel tetrazolium-based assay. *Cancer Res.* (1989) 49:4435-4440.
109. Purdie et al., Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. *Survey of Women's Health Study Group. Int J Cancer* (1995) 62:678-84.
110. Rasmussen et al., Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies. *Am J Epidemiol.* (2017) 185(1): 8–20.
111. Reid et al., Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-analysis. *Cancer Epidemiol Biomarkers Prev.* (2011) 20(7):1287-95.
112. Rosenblatt et al., Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control* (2011) 22:737-742.
113. Rosenblatt et al., Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol* (1992) 45:20-5.
114. Rossi et al., Acute inflammatory response secondary to intrapleural administration of two types of talc. *Eur Respir J.* (2010) 35(2):396-401.
115. Schildkraut et al., Association between Body Powder Use and Ovarian Cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev.* (2016) 25(10):1411-7.
116. Shen et al., Risk of uterine, ovarian and breast cancer following pelvic inflammatory disease: a nationwide population-based retrospective cohort study. *BMC Cancer.* (2016) 16(1):839.
117. Shukla et al., Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *Am J Respir Cell Mol Biol.* (July 2009) 41(1):114-23.
118. Sjösten, Ellis & Edelstam, Retrograde migration of glove powder in the human female genital tract. *Hum Reprod.* (2004) 19(4):991-5.
119. Terry et al., Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila).* (2013) 6(8):811-21.
120. Tiourin et al., Tubal Ligation Induces Quiescence in the Epithelia of the Fallopian Tube Fimbria. *Reprod Sci.* (2015) 22(10):1262-71.

- 121.Trabert et al., Aspirin, Nonaspirin Nonsteroidal Anti-inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst.* (2014) 106(2):djt431.
- 122.Trabert et al., Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. *Gyn. Onc.* (2014) 135:297-304.
- 123.Tzonou et al., Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer* (1993) 55:408-10.
- 124.Venter & Iturralde, Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *S Afr Med J.* (1979) 55(23):917-9.
- 125.Viskum K, et al. Long term sequelae after talc pleurodesis for spontaneous pneumothorax. *Pneumologie.* (1989) 43:105-6.
- 126.Wentzensen et al., Talc Use and Ovarian Cancer: Epidemiology Between a Rock and a Hard Place. *J Natl Cancer Inst.* (2014) 106(9) DOI:10.1093/njci/dju260.
- 127.Werebe et al., Systemic distribution of talc after intrapleural administration in rats. *Chest.* (1999) 115(1):190-3.
- 128.Whittemore et al., Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol* (1988) 128:1228-40.
- 129.Wong et al., Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol* (1999) 93:372-6.
- 130.Wu et al., Markers of inflammation and risk of ovarian cancer in Los Angeles County, 2009. *Int J Cancer* (2009) 124:1409-1415.
- 131.Wu et al., African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. *Cancer Epidemiol Biomarkers Prev* (2015) 24:1094-1100.
- 132.Zhou et al., Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis. *Cancer Causes Control.* (2017) 28(5):415-428.

APPENDIX A

CURRICULUM VITAE
University of Alabama at Birmingham
School of Medicine Faculty

Date: January 30, 2019

PERSONAL INFORMATION

Name: Michael J. Birrer, MD, PhD
Citizenship: US
Foreign Language(s): None
Home Address: 2024 2nd Avenue N., Unit #1601, Birmingham, AL 35203
Telephone: 617-320-7460 (cell)

RANK/TITLE

Department: Director, Comprehensive Cancer Center
Professor of Medicine, Division of Hematology-Oncology
Professor of Pathology, Obstetrics and Gynecology
Business Address: UAB Comprehensive Cancer Center
1824 Sixth Avenue South, WTI 202
Birmingham, AL 35294-3300
Phone: 205-996-2524
Fax: 205-975-7428
Email: mbirrer@uab.edu

HOSPITAL AND OTHER (NON ACADEMIC) APPOINTMENTS
PROFESSIONAL CONSULTANTSHIPS

8/1/2017-Present	Director, Comprehensive Cancer Center
11/1/2008-7/31/2017	Director, Medical Gynecologic Oncology Director, Gynecologic Cancer Research Program Gillette Center for Gynecologic Oncology, Massachusetts General Hospital Leader, Dana-Farber/Harvard Cancer Center Gynecologic Cancer Program
7/1/2000-10/31/2008	Deputy Branch Chief, Cell and Cancer Biology Branch, CCR, NCI
7/1/1991-10/31/2008	Chief, Molecular Mechanisms Section, Center for Cancer Research, National Cancer Institute
1988-1995	Medical Oncology Consultant to Gynecologic Oncology Tumor Board, National Naval Medical Center
1988-2008	Attending Physician, National Naval Medical Center
1988-2008	Attending Physician, Clinical Center, National Cancer Institute (NCI), Bethesda

EDUCATION

Year	Degree	Institution
8/73-6/76	BS	Rensselaer Polytechnic Institute, Troy, NY Major - Biology, Minor - Philosophy, GPA 3.99 cum Laude
7/76-6/82	MD	Albert Einstein College of Medicine, Bronx, NY
7/76-6/82	MS, PhD	Albert Einstein College of Medicine, Bronx, NY Microbiology and Immunology

Thesis: The Role of Measles Virus in Multiple Sclerosis
Mentor: Dr. Barry Bloom, Chairman, Department of
Microbiology and Immunology

MILITARY

U.S. Public Health Service (Serial No. 59928)

1991	Lieutenant Commander 04
1992	Commander 05
1997	Captain 06 Temporary Grade
2001	Captain 06 Permanent Grade

LICENSURE

1985	Medical License: Maryland
1982	Medical License: Massachusetts #52635

BOARD CERTIFICATION

1982	National Board of Medical Examiners
1985	Diplomate, American Board of Internal Medicine
1987	Diplomate, Subspecialty of Medical Oncology

POSTDOCTORAL TRAINING

7/1/1982-6/30/1983	Internship, Internal Medicine, Massachusetts General Hospital, Boston, MA (Dr. John Potts, Chairman, Department of Medicine)
7/1/1983-6/30/1985	Residency, Internal Medicine, Massachusetts General Hospital, Boston, MA
7/1/1985-6/30/1988	Fellowship, Medical Oncology, Medicine Branch, Clinical Oncology Program, National Cancer Institute, Bethesda, MD (Dr. Robert C. Young, Associate Director, Clinical Oncology Program)

ACADEMIC APPOINTMENTS

Year	Rank/Title Institution
8/1/2018 – Present	UAB appointment to Level II Graduate Faculty
8/1/2017 – Present	Evalina B. Spencer Chair in Oncology
8/1/2017-Present	Professor of Medicine, University of Alabama at Birmingham Division of Hematology-Oncology
11/1/2008-7/31/2017	Professor, Department of Medicine Harvard Medical School, Boston, MA
7/1/1991-10/31/2008	Senior Investigator, National Cancer Institute, NIH
7/1/1988-6/30/1991	Investigator, National Cancer Institute, NIH
1988-1995	Assistant Professor, Uniformed Services University of Health Sciences, Department of Medicine, Naval Hospital, Bethesda, MD
1982-1985	Instructor in Medicine, Harvard Medical School, Boston, MA

AWARDS/HONORS

1973-1976	Dean's List (all semesters)
1976	Phi Lambda Epsilon
1976	Sigma Xi Award

1977-1982	Medical Scientist Training Program (5T32GM7288)
1980	Alpha Omega Alpha, National Medical Honorary Society
1988	Outstanding Performance, Uniformed Services University of Health Sciences
1992	Division of Cancer Prevention and Control Employee of the Month
1992	Public Health Service Achievement Award
1993	Public Health Service Citation
1994	Equal Employment Opportunity Officer's Achievement Award
2010-2016	Best Doctors in America
2010-2016	Top Doctors in Boston, Boston Magazine
2014	Public Service Award, Foundation for Women's Cancer
2015	Director's Service Award, NCI
2016	Claudia Cohen Research Foundation Prize for Outstanding Gynecologic Cancer Researcher

PROFESSIONAL SOCIETIES/ MEMBERSHIPS

1986-1988	American Association of Clinical Oncology
2003-present	American Association of Clinical Oncology
1986-present	American Association for Cancer Research
1989-present	Gynecologic Oncology Group
2001-present	Society of Gynecologic Oncologists
2007-present	International Gynecologic Cancer Society
2011-present	European Society of Medical Oncology

COUNCILS AND COMMITTEES

1988-1991	Clinical Oncology Program, Fellowship Selection Committee, NCI, NCI
1990-1993	Committee for the Protection of Human Subjects, NNMC, Bethesda, MD
1990-1993	Grant Review for Early Detection and Community Oncology Program, DCPC, NCI
1990-2013	Experimental Medicine Committee, Gynecologic Oncology Group (GOG)
1992-present	Division of Cancer Prevention and Control Fellowship Selection Committee, DCPC, NCI
1992-1994	NCI Institutional Review Board for Extramural Affairs, NCI, Bethesda, MD
1993	Planning Committee for International Conference for Colorectal Screening
1994	Chairman, International Conference for Colorectal Screening: New Technology Development Section
1994	Source Evaluation Group for Early Detection Network, DCPC, NCI
1995	Committee for Scientific Diversity, NIH
1995-1999	Medical Oncology Consultant to Gynecologic Oncology Tumor Board, WRAM
1997-2001	Ovarian Cancer Research Program, Department of Defense (DOD)
2000-2001	Chair – Ovarian Cancer Research Program, DOD
2001	Steering Committee, Gynecologic Oncology Faculty, CCR
2001	Pre-Clinical Working Group
2001-2002	Chair Emeritus, Ovarian Cancer Research Program, Intergration Panel DOD
1998-2013	Protocol Development Committee, GOG
2001-2013	Ovarian Committee, GOG
2001-2013	Ancillary Data Committee GOG
2001-2002	Co-Chair, Committee for Experimental Medicine GOG

2002	Gynecologic Cancers Progress Review Group Pre-Meeting with Director
2002	Gynecologic Cancer Progress Review Group Implementation Meeting
2002-present	Chair, Committee for Experimental Medicine GOG
2002-2004	American Society of Clinical Oncology (ASCO) Program Committee Gynecologic Cancer Track
2002-2005	SGO Program Committee Member
2003	GOG Site Visit Committee for Experimental Medicine (priority score 175)
2003	Chair GOG Corporate Scientific Symposium
2003-present	Chairman's Advisory Committee GOG
2004	Member GOG Corporate Scientific Symposium Committee
2005	Program Committee, International Meeting on Ovarian Cancer
2005-2016	Co-Chair, Gynecologic Cancer Steering Committee (GCSC) of the National Institute of Health (NCI)
2006-present	Member, Reproductive Scientific Development Program Board
2009-2011	Chair Translational Science Committee, Gynecologic Cancer Intergroup (GCIG)
2009-2013	TCGA Steering Committee
2009-2016	Co-Chair of the Gynecologic Cancer Steering Committee (GCSC) of the National Institute of Health (NCI)
2009-present	Scientific Board, Target Ovarian Cancer
2010-present	Program for the Assessment of Clinical Cancer Tests (PAACT)
2010-2012	Medical Advisory Board, Illumina
2010-present	Witherspoon Council on Ethics and the Integrity of Science
2011-2014	Member, National Clinical Trial Network Working Group
2011-present	External Advisory Board Clinical Proteomic Tumor Analysis Consortium (CPTAC)
2012-2015	ASCO Program Committee Tumor Biology Track
2012-present	Group Banking Committee
2013-present	Co-Chair, Translational Research Working Group, NRG
2013-present	NRG Research Committee
2014-2015	Clinical Trial Planning Meeting Organizing Committee – Uterine Corpus
2014-2015	Co-chair UPSC CTPM Group 2
2014-present	Chair, NCTN Correlative Science Committee
2015-present	Immunogen GYN Steering Committee for Development of IMGN853
2015-present	Member, Special Commission on Ovarian Cancer, Massachusetts Department of Public Health
2017-2018	SGO Program Committee Member
2018	Cancer Research UK Science Committee Expert Review Panel
2018-present	AL Governor appointment to the Study Commission for Gynecologic Cancers
2018	NCI ZRG1 OTC-W Study Section Review Panel
2018	Review of NCI Intramural Research Programs

UNIVERSITY ACTIVITIES

2000-present	External Advisory Board, MD Anderson Cancer Center Uterine SPORE
2006	Member, Marsha Rivkin Center for Ovarian Cancer Research Grant Review
2008-2013	Chair, External Advisory Board Fox Chase Cancer Center Ovarian SPORE
2008-2017	Member, Cancer Center Leadership Committee, MGH
2009-2013	External Advisory Board, Stanford University Ovarian SPORE

2010-present	Scientific Board, Terry Fox Research Institute - Biomarker Program 'COEUR'
2011-present	External Advisory Board Roswell Park Ovarian SPORE
2012-2017	Member, Academic Advisory Group, MGH
2014-present	Member, Marsha Rivkin Scientific Board

EDITORIAL BOARDS

Disease Markers
 American Journal of Obstetrics and Gynecology
 Women's Health Journal
 Clinical Cancer Research
 Journal of Biologic Chemistry
 Journal of the National Cancer Institute – Associate Editor

EDITORIAL REVIEW

American Journal of Respiratory Diseases, Biochim Biophys Acta, Blood, Cancer, Cancer Research, Gynecologic Oncology, Journal of Clinical Oncology, Journal of the National Cancer Institute, Journal of Obstetrics and Gynecology, Molecular Carcinogenesis, Molecular and Cellular Biology, Oncogene, Proceedings of the National Academy of Sciences, National Science Foundation Grant Review, The Israel Science Foundation

MAJOR RESEARCH INTERESTS

My major research interest is in characterizing the genomics of gynecologic cancers and translating it into improving in the clinical management of these diseases. The research focuses on the development of early detection assays, elucidation of new biology, discovery of novel therapeutic targets, and identification and validation of predictive and prognostic biomarkers. It is our vision that through a better understanding of the molecular underpinnings of these cancers, we will be able to better diagnose and treat these diseases.

TEACHING EXPERIENCE

1988-1995	Medical Student Preceptor, Uniformed Services University of Health Sciences
1991-1993	Lecturer, Clinical Service Lecture Series, NMOB, DCT, NCI
1991-present	Lecturer, Cancer Prevention Fellowship Seminar Series, DCPN, NCI
2010-present	Gynecologic Cancer Academy
2015-present	Member, Thesis Committee MIT Graduate Student

RESEARCH TRAINEES

<u>Name</u>	<u>Position</u>	<u>Position Obtained after Training</u>
Richard Rosenberg, MD	Clinical Associate	Assistant Professor, University of Arizona
Dennis Sanders, MD	Clinical Associate	Assistant Professor, Boston University
Eva Szabo, MD	Clinical Associate	Senior Investigator, NCI
Powel Brown MD, PhD	Clinical Associate	Associate Professor, Dept. of UTS
Steven Lemon, MD	Clinical Associate	Assistant Professor, Creighton University
Anita Sabichi, MD	Clinical Associate	Assistant Professor, MDACC
Rhoda Alani	Howard Hughes Scholar	Massachusetts General Hospital
Michael Teneriello, MD	Gyn Oncology Fellow	Assistant Professor, University of Pittsburgh
Robert Taylor, MD	Gyn Oncology Fellow	Assistant Professor, USUHS
Sung Kim, MD	Fogarty Fellow	Assistant Professor, Seoul Korea

Hiro Dosaka	Fogarty Fellow	Assistant Professor, Sapporo, Japan
Mary Parker, MD	Gyn Oncologist	Tripler Army Base Ha.
Kelly Gendreau	Student Trainee	Colgate University
Tricia Francis	Student Trainee	University of Michigan
Julie Francis	Student Trainee	Harvard University
Daniel Gephart	Student Trainee	University of Michigan
Yatia Gross	Student Trainee	McKinley High School
Achim Moesta	Student Trainee	Colgate University
Robert Kao	MCPS/HHMI	Boston College
Ginger Gardner, MD	GCF Scholar	Mt Sinai
Denver Hendricks, PhD	Fogarty Fellow	Research Associate UCT S.A.
Kristin Zorn, MD	GCF Fellow	University of Oklahoma
Jeff Chick	Colgate University	Colgate University
Will Winter, MD	Gyn Oncology Fellow	Brooks Army Hospital

MAJOR LECTURES AND VISITING PROFESSORSHIPS

1988 Grand Rounds, Clinical Oncology Program, NCI, Bethesda, MD

Grand Rounds, Fox Chase Cancer Center, Philadelphia, PA

1991 *Malignancies of the Aerodigestive Tract*, ICN-UCLA Symposium: Keystone, CO

Department of Head & Neck Cancers, M.D. Anderson Cancer Center, Houston, TX

1992 *Early Detection of Cancer: Challenges for Molecular Biology*, Early Detection Branch, DCPC, NCI, Gaithersburg, MD

Microbiology and Immunology Sem. Series, Medical College of Virginia, Richmond, VA

1993 Laboratory and Branch Chiefs Meeting, DCPC, NCI

Grand Rounds, Clinical Oncology Program, NCI, Bethesda, MD

1994 DCPC Colloquium

1995 *Novel Intervention Agents*, Chairperson, Mini-symposium, AACR, Washington, DC

1996 Department of Biochemistry, University of Cincinnati, Cincinnati, OH

Cancer Symposium, CHEP, Perry Point, MD

1997 Grand Rounds, University of Illinois, Chicago, IL

13th Annual Ella T. Grasso Memorial Conference, University of Connecticut, Farmington, CT

- 2001** Gynecologic Cancer Translational Research Retreat, April
- 2001** *Molecular Prevention Course Oncogenes and Tumor Suppressor Genes*, August
- 2001** Co-Chair Gynecologic Oncology Faculty Retreat
- 2002** *Director's Challenge*, PI Meeting Bethesda MD, Nov 6-8
- 2002** *RTK Inhibitors*, Chair, ASCO Molecular Therapeutics Symposium, San Diego, CA, Nov 8, 2002
International Meeting for Early Ovarian Cancer, Dulles Airport, Washington, D.C.
- 2003** Chair, Thesis Defense Committee Department of Gynecologic Oncology, University of South Florida, Tampa, FL
Ovarian Cancer Biology, Survivor's Course, Society of Gynecologic Oncology Annual Meeting, Miami, FL
Expression Profiling of Ovarian Cancer, Oncogene Meeting, Frederick, MD
Novel Retinoids, Hormonal Carcinogenesis Faculty Meeting, Rocky Point, MD
Expression Profiling of Ovarian Cancer, 19th Annual Ella T. Grasso Memorial Conference, University of Connecticut, Hartford, CT
- 2004** *Expression Profiling of Ovarian Cancer*, Ovarian Cancer Mouse Models Meeting, MMHCC San Juan, Puerto Rico
Expression Profiling of Ovarian Cancer, 1st International, Conference on Ovarian Cancer, Physician Education Resource Co-Organizer, Park Plaza Hotel, New York, NY
Molecular Classification of Ovarian Cancer, Johns Hopkins School of Medicine, Department of Pathology, Baltimore, MD
GOG-SPORE Collaborations, SPORE Annual Meeting, Baltimore MD
Genomic Analysis of Ovarian Cancer, Division of Gynecologic Oncology, University of Alabama, Birmingham, AL
Gynecologic Cancer Intergroup Presentation to the NCI Director, Bethesda, MD
Genomic Comparison of Animal and Human Ovarian Cancer, International Society of Gynecologic Cancer, Edinburgh, Scotland, UK
Preparing for Peer Review Ovarian Cancer Ovarian Cancer National Alliance Washington, DC

NCI Initiatives, Gynecologic Cancer Foundation Allied Health Group Presentation SGO Annual Meeting, Miami, FL

Ovarian Cancer Biology, Survivor's Course, Society for Gynecologic Oncologists Annual meeting, Miami FL

2005 Moderator and Co-organizer, Translational Science Session, 2nd International Conference on Ovarian Cancer, Plaza Hotel, New York, New York

ET-743- a new cytotoxic agent, 2nd International Conference on Ovarian Cancer, Plaza Hotel, New York, NY

Molecular Profiling of Ovarian Cancer Genomics Mini-symposium AACR, Anaheim, CA

GOG Priorities "Omics" Corporate Symposium Gynecologic Oncology Group Semi- Annual Meeting, Baltimore, MD

SPORE Investigator Meeting, Co-Chair, Ovarian Break-Out Group

Co-organizer State of the Science Meeting, Ovarian Cancer, Rockville MD

Moderator, Biomarkers and Phase III Trial Design, State of the Science Mtg., Ovarian Cancer, Rockville, MD

Molecular Etiology, Ovarian Cancer Session, Symposium on Women's Cancer, King Hussein Cancer Center, Amman, Jordan

Chair, Ovarian Cancer Treatment Session, King Hussein Cancer Center, Amman, Jordan

Tissue Based Assays-Con Ovarian Cancer National Alliance Annual Meeting, Atlanta, GA

State of the Science Summary, Ovarian Cancer National Alliance Annual Meeting, Atlanta, GA

The Genomic Analysis of Ovarian Cancer, Ovarian Cancer Symposium, Massachusetts General Hospital Cancer Center, Boston, MA

The Genomic Analysis of Ovarian Cancer, Obstetrics and Gynecology Grand Rounds, Magee Women's Hospital, Pittsburgh, PA

Characterization of a gene signature, which predicts survival in patients with advanced stage, high grade ovarian cancer. Research Seminar, Magee Women's Hospital, Pittsburgh, PA

The Genomics Analysis of Ovarian Cancer: what does it tell us? University of Texas at San Antonio, San Antonio, TX

State of the Science Summary, Gynecologic Cancer Intercrop, Paris, France

2006 GOG Scientific Symposium, *Angiogenesis: A new therapeutic target*. Symposium Chair, San Diego, CA

SPORE-GOG collaborations, Co-Chair SPORE mid-winter meeting, Houston, TX

Whole-Genome Expression Profiling of Papillary Serous Ovarian Cancer: Activated Pathways, Potential Targets and Noise Tri Medicine Meeting, Cambridge Health Technology, San Francisco, CA

Tumor infiltrating lymphocytes in ovarian cancer, Data Club, Cell and Cancer Biology Branch, Bethesda, MD

Focused Plenary Session: *Basic Science and Translational Medicine*, Chair, Society of Gynecologic Oncology Annual Mtg Palm Springs, CA

Translational Science in GOG, Sunrise Session 6: Gynecologic Oncology Group (GOG) Update: What's New in 2006, Society of Gynecologic Oncology Annual Mtg Palm Springs, CA

The Odyssey of Target Identification, Express Postgraduate Course 3: "Targeting Targeted Therapy in Gynecologic Cancers", Society of Gynecologic Oncology Annual Mtg, Palm Springs, CA

Identification of cJun/AP-1 target genes by microarrays and chromatin immunoprecipitation assays: clues to its diverse biologic activities TOIG Seminar, Medical Board Room, Bethesda, MD

Genomic Analysis & The Pathogenesis of Ovarian Cancer Lynn Cohen Foundation Meeting, New York School of Medicine, New York, NY

Translational Science Session, Moderator, Third International Conference on Ovarian Cancer Roosevelt Hotel, New York, NY

Genomic Analysis and Ovarian Cancer Translational Science Session, Third International Conference on Ovarian Cancer Roosevelt Hotel, New York, NY

Disease Classification, 1st International Conference on Ovarian Cancer, Aegean Conference, Crete

Identification of important signaling pathways in serous tumors of the Ovary kCon/fab Annual Meeting, Couran Cove, Australia

Oncogenes and Tumor Suppressor Genes Honors Lecture, University of Cape Town, Cape Town, South Africa

Identification of important signaling pathways in serous tumors of the ovary: a genomic analysis. University of Cape Town, Cape Town, South Africa

Intramural Research Program, Ovarian Cancer National Alliance Annual Meeting, Washington DC

Diagnostics & Imaging in the Management of Ovarian Cancer Second Annual World Oncology Congress, Marriott Marquis, New York, NY

Profile Outcomes Prediction, Second Annual World Oncology Congress, Marriott Marquis, New York, NY

Molecular Biology Session, Chair, State of the Science Mtg Endometrial Cancer, Manchester, UK

Drug Discoveries, 7th Annual International Conference on Ovarian Cancer, MDACC, Houston TX

2007 *LMP/Low grade tumors: are they a unique entity? Molecular Biology Scientific Symposium, GOG Semi-annual Meeting San Diego, CA*

Expression Profiling of Ovarian Cancer: New Insights into its Origin and Novel Therapeutic Targets. Susan Klein Kamen Endowed Lectureship, Memorial Sloan-Kettering Cancer Center, Department of Medicine, New York, NY

New updates from the Ovarian SPOREs, Chair, Post Graduate Session, Society of Gynecologic Oncologists Annual Meeting, San Diego, CA

Expression Profiling of Ovarian Cancer: New Insights on the Origin and Treatment of the Disease, Beijing Symposium: Cell Signaling in Cancer, Development and Stem Cells, Beijing, China

Expression Profiling of Ovarian Cancer: New Insights on the Origin and Treatment of the Disease, The Chinese University of Hong Kong Department of Obstetrics and Gynecology, Hong Kong

SPORE Gynecologic Cancer Breakout Session, Moderator

Expression Profiling of Ovarian Cancer: New Insights on the Origin and treatment of the Disease, Seminar, Massachusetts General Hospital, Boston, MA

Translational Research in Ovarian Cancer: Gynecologic Oncology 5th Group, 5th Korean Gynecologic Oncology Group Meeting, Seoul Korea

Genomic Profiling of Ovarian Cancer: New Insights into Pathobiology, Korean Society of Gynecologic Cancer, Seoul, Korea

2008 *Tumor Assessment, Targeted Therapies, GOG Symposium, Moderator*

Genomics and Proteomics: The Future is Now, GOG Scientific Symposium, Moderator, GOG

Semi-Annual Meeting, San Diego, CA

Genomic Analysis of Ovarian Cancer, Cancer Center Grand Rounds, Massachusetts General Hospital, Boston MA

Genome-Wide Target Discovery in Ovarian Cancer, Keynote Presentation, 1st Ovarian Cancer Action International Conference, London, UK

Moderator, 1st Ovarian Cancer Action International Conference, London, UK

Moderator, Post Graduate Course 2: What's new in the Gynecologic SPOREs, Society of Gynecologic Oncologists, Annual Meeting, Tampa, FL

Genomic Approaches to Target Discovery, Post Graduate Course 4, Society of Gynecologic Oncologists, Annual Meeting, Tampa, FL

The Genomic Revolution: How it will Change the State of the Science of Ovarian Cancer! State of the Science Meeting, Society of Gynecologic Oncologists, Annual Meeting, Tampa, FL

Other Novel Strategies Targeting Cellular Pathways in the Treatment of Advanced Ovarian Cancer, SGO Satellite Symposium, Society of Gynecologic Oncologists, Annual Meeting, Tampa, FL

The Biology of Ovarian Cancer, Survivor's Course Gynecologic Cancer Foundation, Society of Gynecologic Oncologists, Annual Meeting, Tampa, FL

Cancer Stem Cell Gene Signature identified from ovarian tumor side populations, Focused Plenary on Ovarian Cancer, Society of Gynecologic Oncologists, Annual Meeting, Tampa, FL

Genomic Analysis of Ovarian Cancer: where will it lead us? Bench to Bedside AACR Special Meeting, Amman, Jordan

New Agents and Translational Research in Ovarian Cancer Moderator, Fifth International Symposium on Ovarian Cancer and Gynecologic Malignancies New York, NY

Optimal Systemic Therapy for Advanced Uterine Cancer Moderator, Fifth International Symposium on Ovarian Cancer and Gynecologic Malignancies New York, NY

Therapy for a Patient with Platinum Resistant/refractory Recurrent Ovarian Cancer should be selected Based on Result of an In Vitro Extreme drug Sensitivity/Resistance Assay- Con, Fifth International Symposium on Ovarian Cancer and Gynecologic Malignancies New York, NY

Biobehavioral influences on tumor biology: Preclinical models of neuroendocrine regulation, Symposium organizer, Natcher Auditorium, NIH, Bethesda, MD, June 24, 2008

Clinical and Translational Research Opportunities to Expand the Paradigms Biobehavioral

influences on tumor biology: Preclinical models of neuroendocrine regulation, Natcher Auditorium, NIH, Bethesda, MD, June 24, 2008

The Molecular Classification of Ovarian Cancer: survival, resistance, and new targets. 2nd International Conference on Ovarian cancer: State of the Art and Future Directions, Rhodes, Greece June 26, 2008

Ovarian Cancer – Update of Research, Ovarian Cancer National Alliance, Omni Shoreham Hotel, Washington D.C., July 9, 2008

Chaired Session: Translational Science in Gynecologic Cancer, The 12th International Gynecologic Cancer Society, Dusit Thani Hotel, Bangkok, Thailand, October 25 – 28, 2008

Frontiers: Translational Science in Gynecologic Cancer, The 12th International Gynecologic Cancer Society, Dusit Thani Hotel, Bangkok, Thailand, October 25 – 28, 2008

The Biology of Early Ovarian Cancer, GYN-Onc Research Program, Intramural Research Program, NCI, NIH, Bethesda, MD

Survivors Course GCF, Hughes Auditorium, Chicago, Illinois, July 2008

Research Updates, Part I, Ovarian Cancer National Alliance, Omni Shoreham, Washington, DC, July 8, 2008

2009 EOCPP External Advisory Committee Meeting, MSKCC, New York, NY, January 29, 2009

Biological Markers; New Markers for Response, 7th International Symposium Advanced Ovarian Cancer: Optimal Therapy, Update, Valencia, Spain, February 27 & 28, 2009

The Genomics of Ovarian Cancer: What does it tell us? Moreton Grand Rounds, University of Mississippi, Jackson, MS, March 10, 2009

Personalized Medicine: Clarity or Confusion? Alpha Omega Alpha Banquet, University of Mississippi, Jackson, MS, March 10, 2009

Ovarian Congress, New York, NY, March 20-21, 2009

The Genomics of Ovarian Cancer: What does it tell us? Cancer Center Grand Rounds, The Cancer Institute of New Jersey, New Brunswick, NJ, April 8, 2009

New Insights in the Biology and Pathogenesis of Epithelial Ovarian Cancer Gene Expression Profiles in Ovarian Carcinoma in Relation to Phenotype, Chemosensitivity and Prognosis, Nordic Society of Gynecologic Oncology, Stockholm, Sweden, April 23 & 24, 2009

NCRN/GCIG NCI Clinical Trials Planning Meeting, Manchester, England, June 17-19, 2009

GOG/Committee of Experimental Medicine, Chair GOG/Scientific Session Moderator, Baltimore, MD, July 16-19, 2009

The Biology for Ovarian Cancer GOG/Survivors Course, Baltimore, MD, July 16-19, 2009

Stromal–Epithelial Interactions in Ovarian Cancer: Implications for Biology and Treatment, Australia Ovarian Cancer Study, Familia Aspects of Cancer, Cancer and Families: Research and Practice, Queensland, Australia, August 11-14, 2009

Ovarian Cancer, Annual Community Oncology Research Forum, Dallas, Texas, September 11, 2009

Session Debate (Con): All Patients at High Risk for Ovarian Cancer Should Undergo Routine Screening; Session Debate (Con): Therapy for the Patient with Platinum-Resistant/Refractory Recurrent Ovarian Carcinoma Should be Selected Based on the Results of an In Vitro Extreme Drug Sensitivity/Resistance Assay, Fifth Annual Oncology Congress, San Francisco, CA, September 25, 2009

Novel Therapeutics in Clinical Trial, American College of Radiology Imaging Network, Arlington, VA, October 2, 2009

The Biology of Ovarian Cancer, Ovarian Cancer Survivors Course, Gynecologic Cancer Foundation, Washington, D.C., November 7, 2009

GOG Site Visit, Bethesda, MD, November 9-10, 2009

First Global Workshop on Ovarian Cancer, Chicago, IL, November 20 & 21, 2009

2010 *USON GYN CME Meeting, Phoenix, AZ, January 15-16, 2010*

Canadian Ovarian Cancer Research, Toronto, Canada, February 4, 2010

Future Directions in Ovarian Cancer, London, UK, February 11, 2010

The Program for the Assessment of Clinical Cancer Tests (PACCT/CADP) Chicago, IL, April 7, 2010

Stand Up to Cancer/Phosphatidylinositol 3'-Kinase Dream Team, Walter E. Washington Convention Center, Washington, DC, April 16-18, 2010

Gynecologic Malignancy Advisory Board, New York, NY, May 21 & 22, 2010

What are promising targets for future therapeutic approaches? 4th Ovarian Cancer Consensus Conference, Vancouver, Canada, June 23-27, 2010

The Biology of Ovarian Cancer, Ovarian Cancer Survivors Course, Boston, MA, July 15, 2010

The GOG Specimen Bank and Translational Research, GOG Summer Scientific Session, Boston, MA, July 15-18, 2010

DNA Repair, Cancer Education Consortium Annual Workshop (CEC), Lansdowne Conference Center, Leesburg, VA, September 13, 2010

PARP Inhibitors and BRCA 1 / 2 Associated Ovarian Cancers, Ella Grasso Memorial CME Conference, Yale University, New Haven, CT, November 17, 2010

Emerging Therapeutics in Recurrent Disease, SGO Session III, Northwestern University, Chicago, IL, December 4, 2010

2011 *P53 in ovarian cancer and how it might relate to breast cancer*. Breast Cancer Grand Rounds, Massachusetts General Hospital, Boston, MA, January 4, 2011

Innovative Treatments in Ovarian Cancer, Annual Meeting of the Israeli Society for Clinical Oncology and Radiation Therapy, Tel Aviv, Israel, January 12-14, 2011

Innovative Treatment in Ovarian Cancer - Current Status and Future Prospective, Israeli Gynecologic Oncology Society, Tel Aviv, Israel January 12-14, 2011

The Post Cancer Genomic Atlans Era - Where Do We Go from Here? Helene Harris Memorial Trust 12th International Forum on Ovarian Cancer, Miami, FL January 15-19, 2011

GYN Cancer Academy Educational Program, Inaugural Mentor's Meeting, Valencia, Spain, March 31, 2011

Canadian Ovarian Cancer Resources, Montreal, Canada, April 8, 2011

Ovarian Cancer: The Origin and New Therapeutic Targets, Wayne State University Grand Rounds, Detroit, MI, May 24, 2011

A Phase II Trial of Iniparib (BSI-201) in combination with gemcitabine/carboplatin (GC) in patients with platinum-sensitive recurrent ovarian cancer, ASCO Annual Meeting, Chicago, IL, June 3-7, 2011

When is a Predictor Clinically Useful? Omics Meeting, Bethesda, MD, June 23 & 24, 2011

Ovarian Cancer Genetics, Ovarian Cancer Survivors Course, Boston, MA, August 20, 2011

Biomarkers for Ovarian Cancer: Where can they help? Early Detection Research Network (EDRN), Bethesda, MD, September 13-15, 2011

DNA Repair, Cancer Education Consortium, Leesburg, VA, September 25 & 26, 2011

Appointment Panel, Cancer Research, London, UK, September 29, 2011

Ovarian Clinical Trials Planning Committee, Philadelphia, PA, November 2, 2011

Future/Emerging Treatments? Ovarian Cancer Survivor's Course, Houston, TX, December 1, 2011

- 2012** *New Strategies to Identify and Screen Women at Risk for Ovarian Cancer*, GOG Scientific Session, San Diego, CA, January 26-28, 2012

Ovarian Cancer: State of the Science Past, Present and Future, Baylor-MD Anderson Joint Symposium, MD Anderson, Houston, TX, February 3, 2012

Improving Outcomes for Woman with Advanced Ovarian Cancer, GOG-0218, Prague, The Czech Republic, February 11-12, 2012

The Future of Ovarian Cancer Management: Biomarkers in Oncology, Avastin Ovarian Cancer Launch, Prague, The Czech Republic, February 11-12, 2012

The Challenges of Inter and Intra-Tumoral Heterogeneity in the Management of Ovarian Cancer, American Association for Cancer Research (AACR), Chicago, IL, April 2, 2012

Ovarian Cancer: State of the Science, Beth Israel Deaconess Medical Center Grand Rounds, Boston, MA, June 13, 2012

Targeting Genomic Chaos in Gynecologic Oncology, Program Chair for GOG Summer 2012 Scientific Session, 85th Semi-Annual Meeting, Boston, MA July 26, 2012

Recent Advances in Ovarian Cancer Clinical Research, Keynote Speech; *Everything You Ever Wanted to Know about PARP Inhibitors but were Afraid to Ask*, 9th Biennial Ovarian Cancer Research Symposium, Marsha Rivkin Center for Cancer Research, Seattle, WA, September 7, 2012

- 2013** National Cancer Institute (NCI), National Institutes of Health (NIH), U.S. Department of Human Services, NCI Precision Cancer Medicine Working Group, Bethesda, Maryland, January 10, 2013

Report and discussion of assays to guide treatment, Defining Clinical Utility of Molecular Diagnostics for Cancer Treatment, PACCT Meeting, Bethesda, MD, January 11, 2013

Ovarian Cancer Management-On the Front Line, Chair, Scientific Session, GOG Semi-Annual Meeting - San Diego, CA, January 24-27, 2013

Genomic analysis. Keynote Lecture, 9th International Symposium on Advanced Ovarian Cancer: Optimal Therapy, Valencia, Spain, March 2, 2013

Trials and Tribulations of Ovarian Cancer Screening; Early Detection of Ovarian Cancer: Old

Trials and New Biology; 8th EDRN Meeting, Scientific Program Committee Meeting, Bethesda, MD, March 13-14, 2013

Shift in the Treatment Paradigm of Ovarian Cancer, Chennai, Hyderabad, Hyderabad/Mumbai and Mumbai, India, Global Oncology Summit, March 29-April 1, 2013

NCI Group Banking Committee (GBC) Face-to-Face Meeting, Columbus, OH, April 18-19, 2013

The Importance of Correlative Studies in Clinical Trials Translational/Anti-Angiogenesis, 13th Annual Continuing Professional Development Meeting, Toronto, Ontario, April 26, 2013

The Center for the Study of Technology and Society, Witherspoon Council Meeting, 1) contemporary genetics and 2) end-of-life issues, Washington, D.C., May 28, 2013

Chromatin Regulatory Mechanisms in Ovarian Cancer, External Advisory Committee Meeting, Wistar Institute, Philadelphia, PA, May 29, 2013

The Future of Ovarian Cancer Treatment: Personalized Medicine, Ovarian Cancer Survivors Course, New York, NY, June 8, 2013

Gynecologic Cancer Trial Portfolio Presentation, (Ovarian and Corpus/Cervix Presentations) NCI, NCTN Summer Working Group Meeting, Rockville, MD, July 1-2, 2013

State of the Science in Cervical Cancer: Where We Are Today and Where We Need to Go, GOG 87th Semi-Annual Meeting, San Antonio, TX, July 18-20, 2013

GYN Translational Research Organization in Europe, 2nd Gynaecological Cancer Academy (GCA) Workshop, Paris, France, September 4-9, 2013

Harnessing Genomic Data to Guide Proteomic Analysis: Can Expression Profiling Identify Early Detection Biomarkers? 26th EDRN (Early Detection Research Network) Steering Committee Meeting/Data Jamboree, Seattle, WA, September 10-12, 2013

Target Ovarian Cancer Scientific Advisory Board, Discussion Leader, London, UK, October 17, 2013

Current and Emerging Biomarkers and Targets in Ovarian Cancer, 18th International Society of Gynaecological Oncology (ESGO), Liverpool, UK, October 18-19, 2013

Future of Ovarian Cancer Treatment: Personalized Medicine, Foundation for Women's Cancer, Ovarian Cancer Survivors Course, Washington, DC, November 1-2, 2013

Translational Research Report, GOG Chairman's Working Group, Philadelphia, PA, November 4, 2013

Ovarian Cancer: The State of the Science, Grand Rounds, Karmanos Cancer Institute, Detroit MI,

November 21, 2013

Genetic Profiling Uncovers New Therapeutic Approaches to Ovarian Cancer, 22nd Annual Meeting MITO, “From the Macroscopic to the Microscopic: The Evolution in All Treatments for Ovarian Cancer”, Rome, Italy, November 28-29, 2013

2014 GOG/NRG Oncology Semi-Annual Meeting, San Diego, CA, February 6-9, 2014

Clinical Experience with the Combination of Pimasertib and SAR245409, Opening Remarks, Merck Serono & Quintiles Investigator Meeting, MEKi 012 Study Protocol, Rome, Italy, March 5-7, 2014

SGO 45th Annual Meeting on Women’s Cancer, March 22 & 23, 2014 Foundation for Women’s Cancer, Board and Business Meeting, Board of Directors Meeting and receipt of the 2014 Public Service Award, Tampa, FL, March 23, 2014

National Institutes of Health, National Cancer Institute Think Tank, Bethesda, MD, April 16, 2014

Personalized Medicine: Are All Cancers the Same? Foundation for Women’s Cancer, Gynecologic Cancer Survivors Course, Garden City, NY, May 2, 2014

Druggable Targets in Ovarian Cancer, Third Gynaecological Cancer Academy, Stresa, Italy, May 16-17, 2014

Osmotic Micro-Pump as Delivery System for Intraperitoneal Chemotherapy in the Treatment of Advanced Ovarian Cancer, DF/HCC and the Koch Institute, MIT, The Bridge Project Symposium and Networking Event. Award Announcement for team: Michael Cima, K1 Michael Birrer and Marcela Del Carmen. Cambridge, MA, May 22, 2014

Potential Biomarkers for FGFR inhibitor Therapy, May 31, 2014, Discussant; *Meta-Analysis of Public Microarray Databases for Prognostic and Predictive Gene Signatures of Late-Stage Ovarian Cancer*, Poster Presentation; *Molecular Profiling of Rare Uterine Tumors: A Potential Guide to Treatment?* Oral Presentation, ASCO Annual Meeting, Chicago, IL, May 30-June 2, 2014

Personalized Medicine and Cancer, OhioHealth Cancer Conference, Columbus, OH, June 7, 2014

Clinical Applications of the Cancer Gene Atlas (TCGA) in Endometrial Cancer, Nordic Society of Gynaecological Oncology Annual Meeting, Selfoss, Iceland, June 13-14, 2014

GOG/NRG Semi-Annual Meeting, Chicago, IL, July 10-12, 2014

Panel Moderator, “Pre-Operative Factors”, American Brachytherapy Society, Gyn Multi-Disciplinary Summer Symposium, Chicago, IL, July 13, 2014

Welcome and Course Overview; New Therapeutic Agents in Ovarian Cancer: Foundation for

Women's Cancer, Gynecologic Cancer Survivors Course, Wyndham Hotel, Boston, MA, July 26, 2014

The Genomic Analysis of Ovarian Cancer: Where are We? The Wistar Institute, Philadelphia, PA, September 15, 2014

Needs and Challenges in Ovarian Cancer; Overview of Bridge Project Research. "Bridging the Gap in Ovarian Cancer", The Koch Institute for Integrative Cancer Research at MIT, Cambridge, MA, September 16, 2014

What are the Issues for Surgical Trials? Trials in Surgery Workshop; Why Signatures Miss the Goal in Ovarian Cancer. Fourth Gynaecological Cancer Academy, Frankfurt, Germany, September 19-20, 2014

Genomic Analysis of Ovarian Cancer: Where are We? Guest Lecturer, Richard W. TeLinde Lectureship, Grand Rounds, Johns Hopkins Hospital, Baltimore, MD, October 16, 2014

Panel Member, OncLive Peer Exchange for "Updates in Ovarian and Cervical Cancers" filming, Dallas, TX, October 18, 2014

Faculty Member, 10th Annual International Symposium on Ovarian Cancer and Gynecologic Malignancies "Medical Crossfire" filming, Dallas, TX, October 18, 2014

New Therapeutic Targets in Ovarian and Uterine Cancers, Chemotherapy Foundation Symposium: Innovative Cancer Therapy of Tomorrow, The Greenspan Meeting XXXII, Marriott Marquis, New York, NY, November 6, 2014.

Molecular Targeted Therapy for Ovarian Cancer, 30th Annual Ella T. Grasso Memorial Conference, Yale West Campus, Orange, CT, December 3, 2014

2015 *The Impact of Molecular Testing in Therapeutic Decisions in Ovarian Cancer*, 2015 Progress and Controversies in Gynecologic Oncology Conference, Barcelona, Spain, January 17, 2015

Curative Strategies for Primary Disease; Therapies for Driver Mutations Using Genomics to Stratify Patients or to Personalize Care, Ovarian Cancer Action, HHMT (Helen Harris Memorial Trust) 13th International Forum on Ovarian Cancer, Toledo, Spain, January, January 19, 2015

Genomic Analysis of Ovarian Cancer: Where Are We? Invited Speaker, Globeathon to End Women's Cancer, Inova Fairfax Hospital, Falls Church, VA, January 23, 2015

Genomic Expression Signatures to Predict Debulking Status, NRG Oncology Semi-Annual Meeting, Manchester Grand Hyatt, San Diego, CA, February 5, 2015

Endometrial Cancer Session: *From Histologic to Genetic Classification*. Ovarian Cancer Session: *Concepts in the Biology of Ovarian Cancer: The impact of Genetics on Clinical Practice*, Pakistan Society of Clinical Oncology (PSCO) Gynecologic Cancer Symposium, Keynote Speaker and

Panel Member, Advancing Cancer Care, 2015 Women Cancer Meeting, “Current and Future Concepts”, Lahore, Pakistan, February 14, 2015

Future of Ovarian Cancer Treatment: Personalized Medicine, Foundation for Women’s Cancer, Ovarian Cancer Survivors Course, The Kravis Center, Cohen Pavillion, West Palm Beach, FL, February 28, 2015

The Molecular Genetics of Epithelial Ovarian Cancer, 10th International Symposium on Advanced Ovarian Cancer, Optimal Therapy Update, Valencia, Spain, March 6, 2015

Design a New Immunotherapy Trial in Ovarian Cancer: Phase I Plus Translational Research, Fifth Gynaecological Cancer Academy Workshop, Hotel Primus, Valencia, Spain, March 7, 2015

Personalizing Treatment of Ovarian Cancer: Has the Time Finally Arrived? Medscape Oncology Roundtable Filming, New York, NY, March 17, 2015

Ovarian Cancer, 29th Early Detection Research Network (EDRN) Steering Committee Meeting, Atlanta, GA, March 31, 2015

Global Gyn Steering Committee meeting for IMGN853, New York, NY, April 10, 2015

Antiangiogenic therapy in gynecologic malignancies ~ prediction of efficacy, XXIV Scientific Meeting of the AGO, Salzburg, Austria, April 16, 2015

The Genomic and Epigenomic Characteristics of Long-Term survivors of Ovarian Cancer, 8th International Charite-Mayo-Conference, Berlin, Germany, April 18, 2015

The Genomics of Epithelial Ovarian Cancer: Is Impact on the Management of the Disease, Keynote Speaker, International Symposium on Cancer Research at Mackay Memorial Hospital, Taipei, Taiwan, April 25, 2015

Ovarian Cancer State of the Science, Immunogen, Waltham, MA, May 7, 2015

Retrospective analysis of candidate predictive tumor biomarkers for efficacy in the GOG-0218 trial evaluating front-line carboplatin–paclitaxel with or without bevacizumab for epithelial ovarian cancer, Roche Global Ovarian Cancer Advisory Board Meeting, Zurich Switzerland, May 11, 2015

DFHCC Ovarian Cancer Retreat, Co-Chair, Boston, MA, May 13, 2015

State-of-the-Science - Updates on the Molecular Genetics of Ovarian Cancer and Implications on Management. Educational Concepts Group, Satellite Symposium “Optimizing BRCA-Related Ovarian Cancer Treatment: Progress toward Personalized Therapy, ASCO Annual Meeting, Chicago, IL, May 29, 2015

Retrospective analysis of candidate predictive tumor biomarkers (BMs) for efficacy in the GOG-

0218 trial evaluating front-line carboplatin-paclitaxel (CP) ± bevacizumab (BEV) for epithelial ovarian cancer (EOC). ASCO Annual Meeting, Chicago, IL, June 1, 2015

Tumor Biology Co-Chair, Oral Abstract Session, ASCO Annual Meeting, Chicago, IL, June 1, 2015

Ovarian Cancer: The State of the Science, Grand Rounds, The Ohio State University Medical Center, Columbus, OH, June 17-18, 2015

OvaCure Innovation Summit 2015, Copenhagen, Denmark, June 22, 2015

Translational Research on Ovarian Cancer and Biomarkers in Ovarian Cancer, Japanese Society of Medical Oncology 2015, 13th Annual Scientific Meeting (JSMO2015), Sapporo, Japan, July 16-17, 2015

The Future Role of Biologic Predictive Factors in the Management Strategy, Ovarian Cancer Workshop, FDA, Silver Spring, MD, September 3, 2015

Clinical Applications of Molecular and Genetic Predictive Factors in Endometrial Cancer, 19th International Meeting of the European Society of Gynaecological Oncology (ESGO 2015), The Acropolis Congress Center, Nice, France, October 24-27, 2015

The Future Role of Biological Markers in the Surgical Treatment Planning, 19th International Meeting of the European Society of Gynaecological Oncology (ESGO 2015), The Acropolis Congress Center, Nice, France, October 24-27, 2015

Future Direction of Ovarian Cancer Research and Clinical Trials, Keynote Lecture, 53rd Annual Meeting of the Japan Society of Clinical Oncology, Kyoto, Japan, October 29-31, 2015

Maximizing the Impact of Antiangiogenesis in Gynecology Oncology, 33rd Chemo Annual Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow, New York, NY, November 4-6, 2015

Treatment – Focus on Gynecological Cancers, AACR Cancer Health Disparities Conference, Atlanta, GA, November 13-16, 2015

Identification and characterization of mutations in oncogenes and tumor suppressor genes within cancers of the ovary, endometrial and cervix, AACR Cancer Health Disparities Conference, Atlanta, GA, November 13-16, 2015

Can we predict optimal debulking from the laboratory?, 26th National MITO Meeting, Rome, Italy, December 9-11, 2015

2016 *Integration of biomarkers, correlative, imaging,* NCI, Endometrial Cancer Clinical Trials Planning Meeting, Rockville, Maryland, January 7-8, 2016

GYN Developmental Therapeutics/Phase I/Translational Science Workshop, Chair NRG
Oncology Semi-Annual Meeting, Atlanta, GA, January 21-24, 2016

Future of Ovarian Cancer Treatment: Personalized Medicine, Ovarian Cancer Survivors Course,
West Palm Beach, FL, February 20, 2016

GOG Foundation/Partners Retreat, Philadelphia, PA, February 26, 2016

Mechanism of Action of PARP Inhibitors and Drug Resistance, PER Satellite Symposium SGO
Expert Perspectives in PARP Inhibition: Evolving Management Strategies in Ovarian Cancer,
March 19, 2016

Promising Agents and Strategies in Gynecologic Cancers, Research to Practice Satellite
Symposium SGO, March 20, 2016

Biomarkers for Anti-Angiogenic Therapy, Nordic Society of Gynecologic Oncology Roche
Symposium and Annual Meeting, Bergen, Norway, April 7, 2016

New Targets in Ovarian Cancer, ANZGOG Annual Scientific Meeting, Sydney Australia, April
14, 2016

Current and future perspectives of the treatment of gynaecological cancer, Platinum Sponsor
Breakfast: Roche, ANZGOG Annual Scientific Meeting, Sydney Australia, April 15, 2016

Personalised medicine in gynaecological cancers – how do we get there? ANZGOG Annual
Scientific Meeting, Sydney Australia, April 16, 2016

The Molecular Genetics of Epithelial Ovarian Cancer: The Past, Present, and Future
Distinguished Clinicians in Oncology Seminar Series, University Hospital of Lausanne (CHUV),
Switzerland, April 29, 2016

Molecular Origins of Ovarian Cancer Berlin Institute of Health, Clinical Scientist Summer
Symposium on Translational Medicine, July 1-2, 2016

Endometrial Cancer: The Future of Targeted Therapy NRG Oncology Semi-Annual Meeting,
Dallas, TX, July 14-17, 2016

DNA Repair & PARP Inhibitors, University of Mississippi CANCER 2016: ASCO and Other
Highlights, Jackson, MS, August 19, 2016

The Role of Bevacizumab in Gynecologic Cancers, Roundtable Roche Pharmaceuticals, Vietnam,
September 26-30, 2016

Can Patients Be Selected for Anti-Angiogenic Therapy? 16th Biennial Meeting of the International
Gynecologic Cancer Society (IGCS), Lisbon, Portugal, October 29, 2016

Current and Emerging Roles for PARP Inhibition in Ovarian Cancer, 34th Chemo Annual Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow, New York, NY, November 9-10, 2016

The Next Giant Leap: Making the Cancer Moonshot a Reality, Elsevier Cancer Research Panel Discussion, Boston, MA, November 16, 2016

GYN update-work targeting BRCA mutations and DNA pathway repair, Molecular and Precision medicine (MAP) Tumor Board Series, Massachusetts General Hospital Cancer Center, Boston, MA, November 28, 2016

Predicting optimal cytoreduction, ISGO, Translation and Innovation, Dublin, Ireland, December 2, 2016

Novel targets in epithelial ovarian cancer, ISGO, Translation and Innovation, Dublin, Ireland, December 3, 2016

2017 *Ovarian Cancer Translational Science Research: Moving the field forward*, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, January 30, 2017

Can biology predict the role of surgery? – The medical point of view. European Institute of Oncology, Milan, Italy, January 31, 2017

Ovarian Cancer: The State of the Science – Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, February 1, 2017

Ovarian Cancer: The State of the Science, Grand Rounds, The University of Miami, Miami, FL, February 16-17, 2017

How can molecular abnormalities influence our clinical approach, ESMO Advanced Ovarian Cancer, Valencia, Spain, March 2-3, 2017

Dissecting the Decision: Investigators Discuss Available and Emerging Data Shaping the Management of Common Gynecologic Cancers, Research to Practice Satellite Symposium SGO, March 12, 2017

Ovarian Cancer: The State of the Science, Grand Rounds, Stony Brook School of Medicine, Stony Brook, NY, March 28-29, 2017

Long term survivor in ovarian cancer: what are the codes?, 9th International Charite-Mayo-Conference, Berlin, Germany, May 6, 2017

Ovarian Cancer Risk Reduction and Treatment, 8th Biennial Looking Back Facing Forward, Boston, MA, May 13, 2017

Evolving Evidence: Current Methods to Optimize PARP Inhibition in Multiple Lines of Care, PER

PARP Ovarian Symposium: Redfining Ovarian Cancer Treatment Paradigms by Maximizing Therapeutic Outcomes with PARP Inhibitors, Chicago, IL, June 2, 2017

Presidential Lecture, WAGO 2017 Annual Meeting, Rancho, CA, June 16, 2017

PARP Inhibitors & Beyond: New Developments in the Treatment of Ovarian & Breast Cancer, LEERINK Partners 5th Annual Healthcare Insights Conference, Boston, MA, July 11, 2017

Ovarian Cancer: The State of the Science, Grand Rounds, The University of Kansas Medical Center, Kansas City, MO, October 5, 2017

Proteogenomi Translational Research Centers Session, NIH, The Clinical Proteomic Tumor Analysis Consortium (CPTAC 3.0) Steering Committee Meeting, Bethesda, MA, October 10, 2017

PER Oncology Best Practice Parp Ovarian Program, Per Oncology, St. Louis, MO, December 4, 2017

2018 *Biologic Basis of Ovarian Cancer*, GEMSTONE Meeting, Dallas, TX, February 3, 2018

Which Molecular Markers Have the Potential to Influence Treatment Decisions with PARP Inhibitors? Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer, New Orleans, LA, March 24, 2018.

PARP INHIBITORS: Their Role in the Treatment of Ovarian Cancer, Bio Ascend – St. Mary's Medical Center, Langhorn, PA, March 28, 2018.

Relapsed Ovarian Cancer – Platinum-Sensitive, TRM Oncology EPIC Expert Panel, Chicago, IL, April 28, 2018.

Ovarian Cancer Team, CPTAC PI F2F Meeting, Bethesda, MD, May 2, 2018.

Ovarian Cancer: The State of the Science, UAB Surgery-Pathology-Biomedical Engineering Tri Departmental Seminar Series, Birmingham, AL, May 8, 2018.

Deep South Network, UAB Cancer Control and Population Sciences Program, Birmingham, AL, May 23, 2018.

Physician Education Resources, Evolving Applications for PARP Inhibitors in Ovarian Cancer: Building on a Solid Foundation, American Society of Clinical Oncology (ASCO), Chicago, IL, June 3, 2018.

Ovarian Cancer: The State of the Science, Comprehensive Cancer Center Seminar Series, University of Alabama at Birmingham, September 5, 2018.

State of the Art for Precision Medicine in Gyn Cancers, IGCS 17th Biennial Meeting, Kyoto,

Japan, September 15, 2018.

PTRC: Ovarian Cancer Team, CPTAC PI F2F Meeting, Bethesda, MD, October 16, 2018.

Treatment Approaches and Emerging Therapies and Testing, Pfizer Ovarian Cancer Learning Day, Chicago, IL, November 14-15, 2018.

2019 *Investigator Perspectives on the Current and Future Role of PARP Inhibition in the Management of Ovarian Cancer*, RTP Grand Rounds, Wynnwood, PA, January 31, 2019

GRANT SUPPORT (PAST AND CURRENT)

COMPLETED

PI: Baum 5T32GM7288 Medical Scientist Training Program Role:	1977-1982	\$350,000
PI: Torti Five Year Grant from Veterans Administration Department of Defense Role: Co-PI	1988-1993	\$495,000
PI: Birrer Intramural Research Award Role: Principal Investigator	1997-1998	\$ 30,000
PI: Birrer Intramural Research Award Role: Principal Investigator	1991-2001	\$120,000
PI: Boyd CA98027 Director's Challenge Grant Role: Co-PI	2001-2004	\$480,000
(Birrer) MGH Proton Program Income (Federal Share)	10/1/2009-9/30/2010	\$128,560
PI: Sood OC080465 (W81XH-09OCP) Early Events in Ovarian Cancer Pathogenesis Role: Principal Investigator for MGH Site	09/01/2009-08/31/2010	\$ 13,000
PI: Del Carmen Fidelity Non-Profit Management Foundation	11/1/2009-10/31/2010	\$ 50,000

Remote Bold Nan-rod Heating for Ablation of Platinum-
resistant Ovarian Cancer
Role: Co-PI

PI: Birrer Osmotic Micro-pump for Delivery of Chemotherapy After Resection of Advanced Ovarian Cancer Role: Principal Investigator	11/1/2009-10/31/2010	\$ 50,000
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PI: Birrer Phase I/II Study of Carbo & Pralatrexate in Patients with Recurrent Platinum Sensitive Ovarian Cancer, NCCN Role: Principal Investigator	04/01/2010-03/31/11	\$300,000
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PI: Birrer 3U01CA062490 Dana-Farber Cancer Institute Early Clinical Trials of new Anti-Cancer Agents with Phase I Emphasis Role: Principal Investigator	04/01/2010-05/31/2011	\$ 7,874
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PI: Birrer 3P50CA105009-0551 Brigham and Women's Hospital, Inc. DF/HCC Ovarian Cancer SPORE – Admin Core Role: Co- Principal Investigator	08/01/2010-07/31/2011	\$ 22,599
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PI: Godwin Ovarian Cancer Research Foundation, Fox Chase Cancer Center/subaward to MGH Therapeutic Targeting of the Tumor Microenvironment in Ovarian Cancer Role: Principal Investigator	04/01/2009-03/31/2012	\$50,000
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PI: Birrer 5RC4CA 156551-03 ARRA-NIH-NCI National Cancer Institute Geonomic Stratification of Ovarian Cancer Patients	09/27/2010-8/30/2013	\$1,262,809
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PI: Birrer KI-DF/HCC 2013-Team 8-0001 Dana-Farber Cancer Institute Title: Osmotic Micro-pump as Delivery System for Intraperitoneal Chemotherapy in the Treatment of Advanced Ovarian Cancer Role: Principal Investigator	03/01/2013-06/30/2015	\$309,144
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PI: Birrer W81XWH-12-1-0521	09/30/2012-09/29/2015	\$200,000
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DOD OCRP TLA

Title: Identification of a Genomic Signature Predicting for
Recurrence in Early Stage Ovarian Cancer

Role: Principal Investigator

PI: Chabner 05/15/2012-11/30/2016 \$ 50,412

5P30CA006516-48 (Chabner, Bruce A)

Dana-Farber Cancer Institute

DFHCC - Program Leaders

Role: Co-Investigator

PI: Bast 09/02/2010-08/31/2015 \$142,000

2P50CA083639-12 The University of Texas MDACC

Title: Early Detection of Epithelial Ovarian Cancer

Role: Principal Investigator for MGH Site

PI: LIU 04/01/2010-09/30/15 \$ 7,874

NIH CTEP ARRADFHCC Subaward to MGH

Title: A Randomized Trial of Early Palliative Care in Newly
Diagnosed Cancer Patients

Role: Principal Investigator for MGH Site

PI: Birrer 03/22/10 - 01/31/15 \$1,712,199

5R01CA142832-02

NIH-NCI National Cancer Institute

Novel Biomarkers in Ovarian Cancer

Role: Principal Investigator

PI: Disaia 03/09/09-03/08/16 \$11,067

U10CA27469 Disaia

NIH/NCI/GOG subaward to MGH

Mid-Career Investigator Award

The major goals of this project are to Chair of the
Experimental Medicine Committee and Chairman's Advisory
Group of the GOG

Role: Principal Investigator

ACTIVE

PI: Birrer 03/01/2013-02/28/2018 \$282,233

RO1CA169200

NIH-NCI National Cancer Institute

Title: The FGF18/FGFR4 Amplicon: Novel Therapeutic
Biomarkers for Ovarian Cancer

Role: Principal Investigator

PI: Skates 09/24/2010 – 03/31/2021 \$399,746

1U01CA152990-01 (Skates, Steven J) NIH-NCI National Cancer Institute Proteomic, Genetic & Longitudinal Pathways to Ovarian Cancer Biomarker Discovery Role: Co-Principal Investigator		
PI: Birrer 5P30CA013148-45 NIH-NCI National Cancer Institute Comprehensive Cancer Center Core Support Grant Role: Principal Investigator	03/28/97 – 03/31/21	\$3,524,460
PI: Birrer 128F99-IRG-15-174-56-IRG American Cancer Society Institutional Research Grant Role: Principal Investigator	01/01/2016 – 12/31/2018	\$120,000
PI: Birrer W81XWH-15-1-0139 DOD OCRP Polymeric RNAi Micorsponge Delivery Simultaneously Targeting Multiple Genes for Novel Pathway Inhibition of Ovarian Cancer Role: Principal Investigator	10/01/2015 – 09/30/2017	\$300,000
PI: Birrer W81XWH-16-1-0593 DOD OCRP-PA Identification of Novel Ovarian Cancer Oncogenes that Function by Regulating Exosome Function Role: Principal Investigator	09/01/2016 – 08/31/2018	\$250,000
PI: Birrer W81XWH-16-2-0038 DOD OCRP – Outcomes Consortium Award The Genomic, Epigenomic, and Quality-of-Life Characteristics of Long-Term Survivors of Ovarian Cancer Role: Principal Investigator	09/01/2016 – 08/31/2019	\$1,000,000
PI: Birrer NCCN Mechanisms of Sensitivity and Resistance to Mirvetuximab Soravtansine: Ovarian Cancer and Mesothelioma Role: Principal Investigator	04/01/2016 – 09/30/2017	\$79,209
PI: Paulovich	04/01/2017 – 03/31/2022	\$973,291

1U01CA214114-01

NIH-NCI National Cancer Institute
Proteogenomic Studies Aimed at Understanding Ovarian
Tumor Responses to Agents Targeting the DNA Damage

PI: Birrer	10/01/2017 – 09/30/2020	\$597,663
W81XWH-17-1-0225		
DOD OCRP		
Treatment of Recurrent, Platinum-Resistant Ovarian Cancer with Glutaminase 1 and PARP Inhibitors		

OTHER (CLINICAL TRIALS)

09-285 A Phase II, Multi-Center, Single-Arm Study Evaluating Carboplatin/Gemcitabine in Combination with BSI-201 for Platinum-Sensitive Recurrent Ovarian Cancer	11/05/2009	PI	\$501,504.36
09-286 A Phase II, Multi-Center, Single-Arm Study Evaluating Carboplatin/Gemcitabine in Combination with BSI-201 for Platinum-Resistant Recurrent Ovarian Cancer	11/05/2009	PI	\$567,802.90
09-397 The Safety and Efficacy of Combination Therapy With AZD2171 and Temsirolimus in Patients with Recurrent Gynecological Malignancies	01/07/2010	Site PI	\$21,018.00
10-113 Phase II, Study of Carboplatin and Pralatrexate in Patients with Recurrent Platinum Sensitive Ovarian, Fallopian Tube or Peritoneal Cancer	02/26/2010	Co PI	\$61,829.00
10-258 A Phase II, 2-Stage, 2-Arm PIK3CA Mutation Stratified Trial of MK-2206 in Recurrent or Advanced Endometrial Cancer	03/01/2011	Site PI	\$23,074.00
11-057 A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of DMUC5754A Administered Intravenously to Patients with Platinum-Resistant Ovarian Cancer	05/30/2012	Site PI	\$92,529.74
11-228 A Phase II, Multi-Center, Double-Blind, Placebo Controlled, Randomized Study of Ombrabulin in Patients With Platinum-Sensitive Recurrent Ovarian Cancer Treated With Carboplatin/Paclitaxel	07/28/2011	PI	\$53,925.50
11-399 A Randomized Phase II, Non-Comparative Study of The Efficacy of PF-04691502 and PF-05212384 in Patients With Recurrent Endometrial Cancer	02/02/2012	PI	\$6,500.00

12-048 A Phase I/II, Open-label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral Rucaparib in Patients with gBRCA Mutation Breast Cancer or Other Solid Tumor (CO-338-010)	03/20/2014	Co PI	\$54,593.75
12-077 A Phase 1/1b, Multicenter Open-Label, Dose-Escalation and Expansion Study to Evaluate the Safety and Antitumor Activity of MEDI3617, a Human Monoclonal Antibody Directed Against ANG2, as a Single-Agent or in Combination Therapy in Adult Subjects with Advanced Solid Tumors	06/20/2012	PI	\$135,913.00
12-159 A Phase I, Study of the Oral PI3kinase Inhibitor BKM120 and the Oral PARP Inhibitor Olaparib in patients with Recurrent Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer	09/01/2012	Site PI	\$81,249.00
12-292 A Phase II, Safety and Efficacy Study of Ipilimumab Monotherapy Following Completion of Chemotherapy in Recurrent Platinum Sensitive Ovarian Cancer Subjects with Residual Measurable Disease	09/17/2013	Site PI	\$41,230.00
12-312 A Phase I, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics of IMG853 in Adults with Ovarian Cancer and other FOLR1-Positive Solid Tumors	10/01/2012	PI	\$127,255.05
13-026 A Randomized, Controlled, Open-Label, Phase II Trial of SGI-110 and Carboplatin in Subjects with Platinum-Resistant Recurrent Ovarian Cancer	05/09/2013	Site PI	\$ 88,759.63
13-072 A Phase I, Multiple-Dose Study of the Safety and Tolerability of Single Agent REGN421 Administered Every 2 or 3 Weeks in Patients with Advanced Solid Malignancies	02/19/2013	PI	\$50,662.00
13-376 A Phase II, Randomized Double Blind Placebo Controlled Trial of Combination of Pimasertib with SAR245409 or of Pimasertib with SAR245409 Placebo in Subjects with Previously Treated Unresectable Low Grade Ovarian Cancer	11/12/2013	PI	\$10,125.00
13-447 A Randomized, Open-Label, Multicenter, Phase II Trial Evaluating the Safety and Activity of DNIB0600A Compared To Pegylated Liposomal Doxorubicin Administered Intravenously to Patients with Platinum-Resistant Ovarian Cancer (GO28609)	07/09/2013	Site PI	\$78,912.00
13-491 A Phase Ib, Open-Label, Non-randomized Multicenter	11/20/2013	PI	\$12,750.00

Study of Birinapant in Combination with Conatumumab in
Subjects with Relapsed Epithelial Ovarian Cancer, Primary
Peritoneal Cancer or Fallopian Tube Cancer

14-050 A Multicenter, Randomized, Double-Blind, Placebo- 07/22/2014 PI \$177,125.00
Controlled Phase III Study of Rucaparib as Switch Maintenance
Following Platinum-Based Chemotherapy in Patients with
Platinum-Sensitive, High-Grade Serous or Endometoid
Epithelial Ovarian, Primary Peritoneal or Fallopian Cancer

14-263 Phase I, Open-Label, Dose Escalation, Study of the 07/18/2014 PI \$650,490.00
Safety, Tolerability and Pharmacokinetics of DMUC4064A
Administered Intravenously to Patients with Platinum Resistant
Ovarian Cancer or Unresectable Pancreatic Cancer (GO29213)

OTHER (PATENTS)

Inventor	Case #2026-4120 - Dominant-negative deletion mutants of c-Jun and their use in the prevention and treatment of cancer
Inventor	HHS Ref. no. E-095-2007 – Pro-angiogenic genes in ovarian tumor endothelial cell Isolates
Inventor	HHS Ref. No. E-061-2007/0-PCT-02 - Gene expression profile for predicts ovarian cancer patient survival
Inventor	HHS Ref. No. E-060-2007/0-US-01 - A Gene expression profile that predicts ovarian cancer patient response to chemotherapy
Inventor	USA Serial No. 61/803,919, File March 21, 2013 – Methods and systems for treatment of ovarian cancer
Inventor	USA Serial No. 61/644497, Filed May 9, 2012 - Method and drug delivery device for treatment of ovarian cancer

BIBLIOGRAPHY

MANUSCRIPTS

1. Ju G, **Birrer MJ**, Udem S, and Bloom BR. Complementation analysis of measles virus mutants isolated from persistently infected lymphoblast cell lines. J. Virol. 33:1004-1012, 1980.
2. **Birrer MJ**, Bloom BR, and Udem S. Characterization of measles polypeptides by monoclonal antibodies. Virology 108: 381-390, 1981.

3. **Birrer MJ**, Udem S, Nathenson S, and Bloom BR. Antigenic variants of measles virus. *Nature* 293: 67-69, 1981.
4. Minna JD, Battey JF, **Birrer MJ**, Brooks BJ, Cuttitta F, DeGreve J, Gazdar AF, Johnson BE, Nau MM, Sausville EA, Seifter E, and Vinocour M. Chromosomal deletion, gene amplification, alternative processing, and autocrine growth factor production in the pathogenesis of human lung cancer. *Princess Takamatsu Symp.* 17: 109-122, 1986.
5. **Birrer MJ** and Young RC. Differential diagnosis of jaundice in lymphoma patients. *Semin. Liver Dis.* 7: 269-277, 1987.
6. Kaye F, Battey J, Nau M, Brooks B, Seifter E, DeGreve J, **Birrer MJ**, Sausville E, and Minna, J. Structure and expression of human L-myc gene reveal a complex pattern of alternative mRNA processing. *Mol. Cell. Biol.* 8:186-195, 1988.
7. Krystal G, **Birrer MJ**, Way J, Nau M, Sausville E, Thompson C, Minna J, and Battey J. Multiple mechanisms for transcriptional regulation of the myc gene family in small-cell lung cancer. *Mol. Cell. Biol.* 8: 3373-3381, 1988.
8. **Birrer MJ**, Segal S, DeGreve JS, Kaye F, Sausville EA, and Minna JD. L-myc cooperates with ras to transform primary rat embryo fibroblasts. *Mol. Cell. Biol.* 8:2668-2673, 1988.
9. DeGreve J, Battey J, Fedorko J, **Birrer MJ**, Eva G, Kaye F, Sausville E, and Minna J. The human L-myc gene encodes multiple nuclear phosphoproteins from alternatively processed mRNAs. *Mol. Cell. Biol.* 8:4381-4388, 1988.
10. **Birrer MJ** and Minna JD. Molecular genetics of lung cancer. *Semin. Oncol.* 15: 226-235, 1988.
11. Schutte J, Minna JD, and **Birrer MJ**. Deregulated expression of human c-jun transforms primary rat embryo cells in cooperation with an activated c-Ha-ras gene and transforms Rat-1a cells as a single gene. *Proc. Natl. Acad. Sci. USA* 86:2257-2261, 1989.
12. **Birrer MJ**, Raveh L, Dosaka H, and Segal S. A transfected L-myc gene can substitute for c-myc in blocking murine erythroleukemia cell differentiation. *Mol. Cell. Biol.* 9:2734-2737, 1989.
13. Takahashi T, Nau MM, Chib I, **Birrer MJ**, Rosenberg RK, Vinocour M, Levitt M, Pass H, Gazdar AF, and Minna, JD. p53: A frequent target for genetic abnormalities in lung cancer. *Science* 246:491-494, 1989.
14. Minna JD, Schutte J, Viallet J, Thomas F, Kaye FJ, Takahashi T, Nau M, Whang-Peng J, **Birrer MJ**, and Gazdar AF. Transcription factors and recessive oncogenes in the pathogenesis of human lung cancer. *Int. J. Cancer* 4 (Suppl.): 32-34, 1989.
15. **Birrer MJ** and Minna JD. Genetic changes in the pathogenesis of lung cancer. *Annu. Rev. Med.* 40: 305-317, 1989.

16. Bliss DP, Jr, Battey JF, Linnoila RI, **Birrer MJ**, Gazdar AF, and Johnson BE. Expression of the atrial natriuretic factor gene in small cell lung cancer tumors and tumor cell lines. *J. Natl. Cancer Inst.* 82: 305-310, 1990.
17. Dosaka-Akita H, Rosenberg RK, Minna JD, and **Birrer MJ**: A complex pattern of translational initiation and phosphorylation in L-myc proteins. *Oncogene* 6:371-378, 1991.
18. Kim JH, Takahashi T, Chiba I, Park JG, Birrer MJ, Roh JK, Lee HD, Kim J, Minna JD, and Gazdar AF. Occurrence of p53 gene abnormalities in gastric carcinoma tumors and cell lines. *J. Natl. Cancer Inst.* 83:938-943, 1991.
19. Szabo E, Preis LH, Brown PH and **Birrer MJ**: The role of jun and fos gene family members in 12-0-tetradecanoylphorbol-13-acetate induced hemopoietic differentiation. *Cell Growth Differ.* 2:475-482, 1991.
20. Smeal T, Binetruy B, Mercola DA, **Birrer MJ**, and Karin M. Oncogenic and transcriptional cooperation with Ha-Ras requires phosphorylation of c-Jun on serines 63 and 73. *Nature* 354:494-496, 1991.
21. Alani R, Brown P, Binetruy B, Dosaka H, Rosenberg RK, Angel P, Karin, M, and **Birrer MJ**. The transactivating domain of the c-jun proto-oncoprotein is required for cotransformation of rat embryo cells. *Mol. Cell. Biol* 11:6286-6295, 1991.
22. Mulshine JL, Linnoila RI, Treston AM, Scott FM, Quinn K, Avis I, Shaw GL, Jensen SM, Brown P, **Birrer MJ**, and Cuttitta F. Candidate biomarkers for application as intermediate end points of lung carcinogenesis. *J Cell Biochem* 16G (Suppl.): 183-186, 1992.
23. **Birrer MJ**, Alani R, Cuttitta F, Preis LH, Sabichi AL, Sanders DA, Siegfried JM, Szabo E, and Brown PH. Early events in the neoplastic transformation of respiratory epithelium. *J Natl Cancer Inst Monogr* 13:31-38, 1992.
24. Mulshine JL, Linnoila RI, Jensen SM, Magnani JL, Tockman MS, Gupta PK, Scott F S, Avis I, Quinn K, **Birrer MJ** and Cuttitta F. Rational targets for the early detection of lung cancer. . *Natl Cancer Inst Monogr* 13:183-190, 1992.
25. Mulshine JL, **Birrer MJ**, Treston AM, Scott F, Quinn K, Avis, I, and Cuttitta F. Growth factors and other targets for rational application as intervention agents. *Adv Exp Med Biol* 320:81-88, 1992.
26. **Birrer MJ** and Brown PH. Application of molecular genetics to the early diagnosis and screening of lung cancer. *Cancer Res* 52:2658s-2664s, 1992.
27. Bar-Ner M, Messing LT, Cultraro CM, **Birrer MJ**, and Segal S. Regions within the c- myc protein that are necessary for transformation are also required for inhibition of differentiation of murine erythroleukemia cells. *Cell Growth Differ.* 3:183-190, 1992.
28. Barrett J, **Birrer MJ**, Kato GJ, Dosaka-Akita H and Dang CV. Activation domains of L-myc and c-

- myc determine their transforming potencies in rat embryo cells. *Mol. Cell. Biol.* 12:3130-3137, 1992.
29. Brown PB, Alani R, Preis LH, Szabo E, and **Birrer MJ**. Suppression of oncogene- induced transformation by a deletion mutant of c-jun. *Oncogene* 8:877-886, 1993.
 30. Teneriello MG, Ebina M, Linnoila RI, Henry M, Nash JD, Park RC, and **Birrer MJ**. p53 and Ki-ras gene mutations in epithelial ovarian neoplasms. *Cancer Res.* 53:3103-3108, 1993.
 31. Mulshine JL, Treston AM, Brown PH, **Birrer MJ**, and Shaw GL. Initiators and promoters of lung cancer. *Chest* 103(1 Suppl) 4S-11S, 1993.
 32. Sabichi AL and **Birrer MJ**: The molecular biology of lung cancer: application to early detection and prevention. *Oncology (Hunting)* 7:19-26; discussion 31-32, 37, 1993.
 33. Kurie JM, Brown P, Salk E, Scheinberg D, **Birrer MJ**, Deutsch P, and Dmitrovsky E. Cooperation between retinoic acid and phorbol esters enhances human teratocarcinoma differentiation. *Differentiation* 54:115-122, 1993.
 34. Szabo E, **Birrer MJ**, and Mulshine JL. Early detection of lung cancer. *Semin. Oncol.* 20:374-382, 1993.
 35. Brown PH, Chen TK, and **Birrer MJ**. Mechanism of action of a dominant-negative mutant of c-Jun. *Oncogene* 9:791-799, 1994.
 36. Domann FE, Levy JP, **Birrer MJ**, and Bowden GT. Stable expression of a c-JUN deletion mutant in two malignant mouse epidermal cell lines blocks tumor formation in nude mice. *Cell Growth Differ.* 5:9-16, 1994.
 37. Dong Z, **Birrer MJ**, Watts RG, Matrisian LM, and Colburn NH. Blocking of tumor promoter-induced AP-1 activity inhibits induced transformation in JB6 mouse epidermal cells. *Proc. Natl. Acad. Sci. USA* 91:609-613, 1994.
 38. Petrak D, Memon SA, **Birrer MJ**, Ashwell JD, and Zacharchuk CM. A dominant negative mutant of c-jun inhibits NF-AT transcriptional activity and prevents IL-2 gene transcription. *J. Immunol.* 153:2046-2051, 1994.
 39. Rapp UR, Troppmair J, Beck T, and **Birrer MJ**. Transformation by raf and other oncogenes renders cells differentially sensitive to growth inhibition by a dominant negative c-jun mutant. *Oncogene* 9:3493-3498, 1994.
 40. Taylor RR, Teneriello MG, Nash JD, Park RC, and **Birrer M**. The molecular genetics of gynecological malignancies. *Oncology (Huntingt)* 8:63-70, 73; discussion 73,78-82, 1994.
 41. Szabo E, Preis LH, and **Birrer MJ**. Constitutive cJun expression induces partial macrophage differentiation in U-937 cells. *Cell Growth Differ.* 5:439-446, 1994.

42. Taylor RR, Linnoila RI, Gerardts J, Teneriello MG, Nash JD, Park RC, and **Birrer MJ**. Abnormal expression of the retinoblastoma gene in ovarian neoplasms and correlation to p53 and K-ras mutations. *Gynecol. Oncol.* 58:307-311, 1995.
43. Draoui M, Chung P, Park M, **Birrer MJ**, Jakowlew S, and Moody TW. Bombesin stimulates c-fos and c-jun mRNAs in small cell lung cancer cells. *Peptides* 16:289-292, 1995.
44. Watts RG, Ben-Ari ET, Bernstein LR, **Birrer MJ**, Winterstein D, Wendel E, and Colburn NH. c-jun and multistage carcinogenesis: association of overexpression of introduced c-jun with progression toward a neoplastic endpoint in mouse JB6 cells sensitive to tumor promoter-induced transformation. *Mol. Carcinog.* 13:27-36, 1995.
45. Cippitelli M, Sica A, Viggiano V, Ye J, Ghosh P, **Birrer MJ**, and Young HA. Negative transcriptional regulation of the interferon-gamma promoter by glucocorticoids and dominant negative mutants of c-Jun. *J. Biol. Chem.* 270:12548-12556, 1995.
46. Lengye E, Singh B, Gum R, Nerlov C, Sabichi A, **Birrer MJ**, and Boyd D. Regulation of urokinase-type plasminogen activator expression by the v-mos oncogene. *Oncogene* 11:2639-2648, 1995.
47. **Birrer MJ**. Translational research and epithelial carcinogenesis: molecular diagnostic assays now--molecular screening assays soon? [editorial; comment]. *J. Natl. Cancer Inst.* 87:1041-1043, 1995.
48. Kim S, Brown PH, and **Birrer MJ**. The inhibitory activity of a transdominant c-jun mutant fused to the ligand binding domain of the estrogen receptor. *Oncogene* 12:1043-1053, 1996.
49. Freemerman AJ, Turner AJ, **Birrer MJ**, Szabo E, Valerie K, and Grant S. Role of c-jun in human myeloid leukemia cell apoptosis induced by pharmacological inhibitors of protein kinase C. *Mol. Pharmacol.* 49:788-795, 1996.
50. Antinore MJ, **Birrer MJ**, Patel D, Nader L, and McCance DJ. The human papillomavirus type 16 E7 gene product interacts with and trans-activates the AP1 family of transcription factors. *Embo J.* 15:1950-1960, 1996.
51. Chen TK, Smith LM, Gebhardt DK, **Birrer MJ**, and Brown PH. Activation and inhibition of the AP-1 complex in human breast cancer cells. *Mol. Carcinog.* 15:215-226, 1996.
52. Verheij M, Bose R, Lin XH, Yao B, Jarvis WD, Grant S, **Birrer MJ**, Szabo E, Zon LI, Kyriakis JM, Haimovitz-Friedman A, Fuks Z, and Kolesnick RN. Requirement for ceramide-initiated SAPK/JNK signalling in stress-induced apoptosis. *Nature* 380:75-79, 1996.
53. Szabo E, Riffe ME, Steinberg SM, **Birrer MJ**, and Linnoila RI. Altered cJUN expression: an early event in human lung carcinogenesis. *Cancer Res.* 56:305-315, 1996.
54. Zia H, Hida T, Jakowlew S, **Birrer MJ**, Gozes Y, Reubi JC, Fridkin M, Gozes I, and Moody TW.

Breast cancer growth is inhibited by vasoactive intestinal peptide (VIP) hybrid, a synthetic VIP receptor antagonist. *Cancer Res.* 56:3486-3489, 1996.

55. Draoui M, Hida T, Jakowlew S, **Birrer MJ**, Zia F, and Moody TW. PACAP stimulates c-fos mRNAs in small cell lung cancer cells. *Life Sci.* 59:307-313, 1996.
56. Brown PH, Kim SH, Wise SC, Sabichi AL, and **Birrer MJ**. Dominant-negative mutants of cJun inhibit AP-1 activity through multiple mechanisms and with different potencies. *Cell Growth Differ.* 7:1013-1021, 1996.
57. Smith LM and **Birrer MJ**. Use of transcription factors as agents and targets for drug development. *Oncology (Huntingt)* 10:1532-1538; discussion 1541-1542, 1996.
58. Grant S, Freemerman AJ, **Birrer MJ**, Martin AH, Turner AJ, Szabo E, Chelliah J, and Jarvis WD. Effect of 1- β -D-arabinofuranosylcytosine on apoptosis and differentiation in human monocytic leukemia cells (U937) expressing a c-Jun dominant-negative mutant protein (TAM67). *Cell Growth Differ.* 7:603-613, 1996.
59. Sabichi AL and **Birrer MJ**. Regulation of nuclear oncogenes expressed in lung cancer cell lines. *J. Cell. Biochem.* 24 (Suppl.):218-227, 1996.
60. Parker MF, Arroyo GF, Geradts J, Sabichi AL, Park RC, Taylor RR, and **Birrer MJ**. Molecular characterization of adenocarcinoma of the cervix. *Gynecol. Oncol.* 64:242-251, 1997.
61. Potapova O, Haghighi A, Bost F, Liu C, **Birrer MJ**, Gjerset R, and Mercola D. The Jun kinase/stress-activated protein kinase pathway functions to regulate DNA repair and inhibition of the pathway sensitizes tumor cells to cisplatin. *J. Biol. Chem.* 272:14041-14044, 1997.
62. Hendricks DT, Taylor R, Reed M, and **Birrer MJ**. FHIT gene expression in human ovarian, endometrial, and cervical cell lines. *Cancer Res.* 57:2112-2115, 1997.
63. Smith LM, **Birrer MJ**, Stampfer MR, and Brown PH. Breast cancer cells have lower activating protein 1 transcription factor activity than normal mammary epithelial cells. *Cancer Res.* 57:3046-3054, 1997.
64. Pisegna JR, Leyton J, Coelho T, Hida T, Jakowlew S, **Birrer MJ**, Fridkin, M, Gozes, I, and Moody, TW. PACAP hybrid: a new PACAP receptor antagonist. *Life Sci.* 61:631-639, 1997.
65. Zhao B, Yu W, Qian M, Simmons-Menchaca M, Brown P, **Birrer MJ**, Sanders BG, and Kline K. Involvement of activator protein-1 (AP-1) in induction of apoptosis by vitamin E succinate in human breast cancer cells. *Mol. Carcinog.* 19:180-90, 1997.
66. **Birrer MJ**. Discoveries in the cell cycle and ovarian cancer [editorial]. *Gynecol. Oncol.* 64:187-188, 1997.
67. Jarvis WD, Fornari FA Jr, Auer KL, Freemerman AJ, Szabo E, **Birrer MJ**, Johnson CR, Barbour

- SE, Dent P, and Grant S. Coordinate regulation of stress-and mitogen-activated protein kinases in the apoptotic actions of ceramide and sphingosine. *Mol. Pharmacol.* 52:935-947, 1997.
68. Hall KL, Teneriello MG, Taylor RR, Lemon S, Ebina M, Linnoila RI, Norris JH, Park RC, and **Birrer MJ**. Analysis of Ki-ras, p53, and MDM2 genes in uterine leiomyomas and leiomyosarcomas. *Gynecol. Oncol.* 65:330-335, 1997.
 69. Szabo E, Francis J, and **Birrer MJ**. Alterations in differentiation and apoptosis induced by bufalin in cJun overexpressing U-937 cells. *Int. J. Oncol.* 12:403-409, 1998.
 70. Zagariya A, Mungre S, Lovis R, **Birrer MJ**, Ness S, Thimmapaya B, and Pope R. Tumor necrosis factor alpha gene regulation: enhancement of C/EBP beta-induced activation by c-Jun. *Mol. Cell. Biol.* 18:2815-2824, 1998.
 71. Carter S, Auer KL, Reardon DB, **Birrer MJ**, Fisher PB, Valerie K, Schmidt-Ulrich R, Michelson R, and Dent P. Inhibition of the mutagen activated protein (MAP) kinase cascade potentiates cell killing by low dose ionizing radiation in A431 human squamous carcinoma cells. *Oncogene* 16:2787-96, 1998
 72. Wise SC, Burmeister LA, Zhou XF, Bubulya A, Oberfield JL, **Birrer MJ**, Shemshedini L. Identification of domains of c-Jun mediating androgen receptor transactivation. *Oncogene* Apr 16;16(15):2001-199.
 73. Jacobs-Helber SM, Wickrema A, **Birrer MJ**. Sawyer ST AP1 regulation of proliferation and initiation of apoptosis in erythropoietin-dependent erythroid cells. *Mol Cell Biol* Jul;18(7):3699-707, 1998 Auer, K.L., 74.
 74. Contessa J, Brenz-Verca S, Pirola L, Rusconi S, Cooper G, Abo A, Davis RJ, Wymann MP, **Birrer MJ** and Dent P. Stimulation of DNA synthesis in primary cultures of rat hepatocytes by multiple agonists via a Ras/Rac-Cdc42/SEK/JNK/c-Jun dependent mechanism. *Mol. Cell. Biol.* 9:561-73, 1998.
 75. Sabichi AL, Hendricks DT, Bober MA, and **Birrer MJ**. Retinoic acid receptor expression and growth inhibition of gynecologic cancer cells by the synthetic retinoid N-(4- hydroxyphenyl) retinamide. *J. Natl. Cancer Inst.* 90:597-605, 1998.
 76. Leyton J, Coelho T, Coy DH, Jakowlew S, **Birrer MJ**, Moody TW. PACAP(6-38) inhibits the growth of prostate cancer cells. *Cancer Lett* 1998 Mar 13;125(1-2):131-9.
 77. Yu W, Simmons-Menchaca M, You H, Brown P, **Birrer MJ**, Sanders BG, and Kline K. RRR - tocopheryl succinate induces prolonged activation of c-jun amino-terminal kinase (JNK) and c-jun induction of apoptosis in human MDA-MB-435 breast cancer cells. *Mol. Carcinog.* 22:247-57, 1998.
 78. Dent P, Jarvis WD, **Birrer MJ**, Fisher PB, Schmidt-Ulrich RK, Grant S. The roles of signaling by the p42/p44 mutagen-activated protein (MAP) kinase pathway; a potential route to radio- and

chemo-sensitization of tumor cells resulting in the induction of apoptosis and loss of clonogenicity: *Leukemia* 1998 Dec;12(12):1843-50.

79. Rao GN, Katki KA, Madamanchi NR, Wu Y, **Birrer MJ**. JunB forms the majority of the AP-1 complex and is a target for redox regulation by receptor tyrosine kinase and G protein-coupled receptor agonists smooth muscle cells. *J Biol Chem*. 1999 Feb 26; 274(9):6003-10.
80. Geradts J, Maynard R, **Birrer MJ**, Hendricks D, Abbondanzo SL, Fong KM, Barrett JC, Lombardi DP. Frequent loss of KAI1 expression in squamous and lymphoid neoplasms. An immunohistochemical study of archival tissues. *Am J Pathol*. 1999 Jun;154(6):1665-71.
81. Wang N, Verna L, Hardy S, Zhu Y, Ma KS, **Birrer MJ**, Stermerman MB. c-Jun triggers apoptosis in human endothelial cells. *Circ Res*. 1999 Sep 3;85(5):387-93.
82. **Birrer MJ**, Hendricks D, Farley J, Sundborg MJ, Bonome T, Walts MJ, Geradts J. Abnormal Fhit expression in malignant and premalignant lesions of the cervix. *Cancer Res*. 1999 Oct 15;59(20):5270-4.
83. Smith LM, Wise SC, Hendricks DT, Sabichi AL, Bos T, Reddy P, Brown PH, **Birrer MJ**. cJun overexpression in MCF-7 breast cancer cells produces a tumorigenic, invasive and hormone resistant phenotype. *Oncogene*. 1999 Oct 28;18(44):6063-70.
84. Johnson AC, Murphy BA, Matelis CM, Rubinstein Y, Piebenga EC, Akers LM, Neta G, Vinson C, **Birrer MJ**. Activator protein-1 mediates induced but not basal epidermal growth factor receptor gene expression. *Mol Med*. 2000 Jan;6(1):17-27.
85. Park JS, Boyer S, Mitchell K, Gilfor D, **Birrer MJ**, Darlington G, El Deiry W, Firestone GL, Munger K, Band V, Fisher PB, Dent P. Expression of human papilloma virus E7 protein causes apoptosis and inhibits DNA synthesis in primary hepatocytes via increased expression of p21(Cip-1/WAF1/MDA6). *J Biol Chem* 2000 Jan 7;275(1):18-28.
86. Cartee L, Vrana JA, Wang Z, Park JS, **Birrer MJ**, Fisher PB, Grant S, Dent P. Inhibition of the mutagen activated protein kinase pathway potentiates radiation-induced cell killing via cell cycle arrest at the G2/M transition and independently of increased signaling by the JNK/c-Jun pathway. *Int J Oncol* 2000 Feb;16(2):413-22.
87. Liu H, Sidiropoulos P, Song G, Pagliari LJ, **Birrer MJ**, Stein B, Anrather J, Pope RM. TNF-alpha g expression in macrophages: regulation by NF-kappa B is independent of c-Jun or C/EBP beta. *J Immunol* 2000 Apr 15;164(8):4277-85.
88. Schmitz MJ, Hendricks DT, Farley J, Taylor RR, Geradts J, Rose GS, **Birrer MJ**. p27 and cyclin D1 abnormalities in uterine papillary serous carcinoma. *Gynecol Oncol*. 2000 Jun;77(3):439-45.
89. Farley J, Gray K, Nycum L, Prentice M, **Birrer MJ**, Jakowlew SB. Endocervical cancer is associated with an increase in the ligands and receptors for transforming growth factor-beta and a contrasting decrease in p27(Kip1). *Gynecol Oncol*. 2000 Aug;78(2):113-22.

90. Rinehart-Kim J, Johnston M, **Birrer MJ**, Bos T. Alterations in the gene expression profile of MCF-7 breast tumor cells in response to c-Jun. *Int J Cancer*. 2000 Oct 15;88(2):180-90.
91. Farley JH, Nycum LR, **Birrer MJ**, Park RC, Taylor RR. Age-specific survival of women with endometrioid adenocarcinoma of the uterus. *Gynecol Oncol*. 2000 Oct;79(1):86-9.
92. Paasinen-Sohns A, Kielosto M, Kaariainen E, Eloranta T, Laine A, Janne OA, **Birrer MJ**, Holtta E. c-Jun activation-dependent tumorigenic transformation induced paradoxically by over expression or block of S-adenosylmethionine decarboxylase. *J Cell Biol*. 2000 Nov 13;151(4):801-10.
93. Vos MD, Ellis CA, Bell A, **Birrer MJ**, Clark GJ. Ras uses the novel tumor suppressor RASSF1 as an effector to mediate apoptosis. *J Biol Chem*. 2000 Nov 17;275(46):35669-72.
94. Kim JS, Pirnia F, Choi YH, Nguyen PM, Knepper B, Tsokos M, Schulte TW, **Birrer MJ**, neuroectodermal tumor cell line in association with RB down-regulation and loss of the G1 checkpoint. *Oncogene*, 2000 Dec 7;19(52):6082-90.
95. Ebina M, Martinez A, **Birrer MJ**, Ilona Linnoila R. In situ detection of unexpected patterns of mutant p53 gene expression in non-small cell lung cancers. *Oncogene*. 2001 May 3;20(20):2579-86.
96. Nycum LR, Smith LM, Farley JH, Kost ER, Method MW, **Birrer MJ**. The Role of p27 in Endometrial Carcinoma. *Gynecol Oncol*. 2001 May;81(2):242-6.
97. Calvisi DF, Donninger H, Vos MD, **Birrer MJ**, Gordon L, Leaner V, Clark GJ. NORE1A tumor suppressor candidate modulates p21CIP1 via p53. *Cancer Res*. 2009 Jun 1;69(11):4629-37.
98. Fan M, Goodwin ME, **Birrer MJ**, Chambers TC. The c-Jun NH(2)-terminal protein kinase/AP-1 pathway is required for efficient apoptosis induced by vinblastine. *Cancer Res*. 2001 Jun 1;61(11):4450-8.
99. Krivak TC, McBroom JW, Seidman J, Venzon D, Crothers B, MacKoul PJ, Rose GS, Carlson JW, **Birrer MJ**. Abnormal fragile histidine triad (FHIT) expression in advanced cervical carcinoma: a poor prognostic factor. *Cancer Res*. 2001 Jun 1;61(11):4382-5.
100. Gardner GJ, **Birrer MJ**. Ovarian tumors of low malignant potential: Can molecular biology solve this enigma? *J Natl Cancer Inst*. 2001 Aug 1;93(15):1122-3.
101. Manzano RG, Montuenga LM, Dayton M, Dent P, Kinoshita I, Vicent S, Gardner GJ, Nguyen P, Choi YH, Trepel J, Auersperg N, **Birrer MJ**. CL100 expression is down-regulated in advanced epithelial ovarian cancer and its re-expression decreases its malignant potential. *Oncogene*. 2002 Jun 27; 21(28):4435-47.
102. Bowen C, **Birrer MJ**, Gelmann EP. Retinoblastoma Protein-mediated Apoptosis After gamma - Irradiation *J Biol Chem*. 2002 Nov 22;277(47):44969-79.

103. Quong J, Eppenberger-Castori S, Moore D 3rd, Scott GK, **Birrer MJ**, Kueng W, Eppenberger U, Benz CC. Age-dependent changes in breast cancer hormone receptors and oxidant stress markers. *Breast Cancer Res Treat.* 2002 Dec; 76(3):221-36.
104. Farley J, Smith LM, Darcy KM, Sobel E, O'Connor D, Henderson B, Morrison LE, **Birrer MJ**, Gynecologic Oncology Group. Cyclin E expression is a significant predictor of survival in advanced, suboptimally debulked ovarian epithelial cancers: a Gynecologic Oncology Group study. *Cancer Res.* 2003 Mar 15; 63(6):1235-41.
105. Dent P, Qiao L, Gilfor D, **Birrer MJ**, Grant S, Fisher PB. The regulation of tumor suppressor genes by oncogenes *Methods Mol Biol.* 2003 222:269-92.
106. Shen YH, Godlewski J, Zhu J, Sathyanarayana P, Leaner V, **Birrer MJ**, Rana A, Tzivion G. Cross-talk between JNK/SAPK and ERK/MAPK pathways: sustained activation of JNK blocks ERK activation by mitogenic factors. *J Biol Chem.* 2003 278(29):26715-21. Epub 2003 May 08.
107. Kinoshita I, Leaner V, Katabami M, Manzano RG, Dent P, Sabichi A, **Birrer MJ**. Identification of cJun- responsive genes in Rat-1a cells using multiple techniques: increased expression of stathmin is necessary for cJun-mediated anchorage-independent growth. *Oncogene.* 2003 May 8;22(18):2710-22.
108. Leaner VD, Kinoshita I, **Birrer MJ**. AP-1 complexes containing cJun and JunB cause cellular transformation of Rat1a fibroblasts and share transcriptional targets. *Oncogene.* 2003 Aug 28;22(36):5619-29.
109. Trepel J, **Birrer MJ**. A Link Between Histone Deacetylase Inhibitors and NF- kappaB Signaling. *Cell Cycle.* 2003 Sep-Oct; 2(5):452-3. No abstract available.
110. Winter WE, Seidman JD, Krivak TC, Chauhan S, Carlson JW, Rose GS, **Birrer, MJ**. Clinicopathological analysis of c-kit expression in carcinosarcomas and leiomyosarcomas of the uterine corpus. *Gynecol Oncol.* 2003 Oct;91(1):3-8.
111. Romashko J, Horowitz S, Franek WR, Palaia T, Miller EJ, Lin A, **Birrer MJ**, Scott W, Mantell LL. MAPK pathways mediate hyperoxia-induced oncotic cell death in lung epithelial cells. *Free Radic Biol Med.* 2003 Oct 15;35(8):978-93.
112. Zorn KK, Jazaeri AA, Awtrey CS, Gardner GJ, Mok SC, Boyd J, **Birrer MJ**. Choice of normal ovarian control influences determination of differentially expressed genes in ovarian cancer expression profiling studies. *Clin Cancer Res.* 2003 Oct 15; 9(13):4811-8.
113. Farley JH, **Birrer MJ**. Biologic directed therapies in gynecologic oncology. *Curr Oncol Rep.* 2003 Nov; 5(6):459-67.
114. Zeinoun Z, Teugels E, Vermeij J, Neyns B, **Birrer MJ**, De Greve J. Restoration of an impaired TGF-beta1 autocrine growth-inhibitory circuit results in growth inhibition of ovarian epithelial cancer cells and complete inhibition of their tumorigenicity. *Cancer Detect Prev.* 2003; 27(5):380-8.

115. Farley J, Uyehara C, Hashiro G, Belnap C, **Birrer MJ**, Salminen E. Cyclooxygenase-2 expression predicts recurrence of cervical dysplasia following loop electrosurgical excision procedure. *Gynecol Oncol.* 2004 Feb; 92(2):596-602.
116. Liu S, Brown CW, Berlin KD, Dhar A, Guruswamy S, Brown D, Gardner GJ, **Birrer MJ**, Benbrook DM. Synthesis of flexible sulfur-containing heteroarotinoids that induce apoptosis and reactive oxygen species with discrimination between malignant and benign cells. *J Med Chem.* 2004 Feb 12; 47(4):999-1007.
117. Hommura F, Katabami M, Leaner VD, Donninger H, Sumter TF, Resar LM, **Birrer MJ**. HMG-I/Y is a c-Jun/activator protein-1 target gene and is necessary for c-Jun-induced anchorage-independent growth in Rat1a cells. *Mol Cancer Res.* 2004 May; 2(5):305-14.
118. Cuello M, Coats AO, Darko I, Ettenberg SA, Gardner GJ, Nau MM, Liu JR, **Birrer MJ**, Lipkowitz S. N-(4-hydroxyphenyl) retinamide (4HPR) enhances TRAIL-mediated apoptosis through enhancement of a mitochondrial-dependent amplification loop in ovarian cancer cell lines. *Cell Death Differ.* 2004 May; 11(5):527-41.
119. Zou X, Jordan RC, Mok S, **Birrer MJ**, Wong DT. DNA copy number abnormality of oral squamous cell carcinoma detected with cDNA array-based comparative genomic hybridization. *Cancer Genet Cytogenet.* 2004 May; 151(1):90-2.
120. Kielosto M, Nummela P, Katainen R, Leaner V, **Birrer MJ**, Holtta E: Reversible regulation of the transformed phenotype of ornithine decarboxylase- and ras-overexpressing cells by dominant-negative mutants of c-Jun. *Cancer Res.* 2004 Jun 1;64(11):3772-9.
121. Sherman, ME, Berman, J., **Birrer, MJ**, Cho KR, Ellenson, LH, Gorstein, F, and Seidman, JD. Current challenges and opportunities for research on borderline ovarian tumors. *Human Pathology* 2004 Aug; 35(8):961-70.
122. Elagib KE, Xiao M, Hussainin IM, Delehanty LL, Palmer LA, Racke FK, **Birrer MJ**, McDevitt MA, and Goldfarb AN. Jun blockage of erythropoiesis: a role for repression of GATA-1 by HERP2. *Mol. Cell. Biol* 2004 Sep; 24(17):7779-94.
123. Donninger H, Bonome T, Radonovich M, Pise-Masison CA, Brady J, Shih J, Barrett JC, and **Birrer MJ**. Whole genome expression profiling of advance stage papillary serous ovarian cancer reveals activated pathways. *Oncogene* 2004 Oct21;23(49):8065-77.
124. Tsuda H, Bandera CA, **Birrer MJ**, Hashiguchi Y, Berkowitz RS, Mok SC. Cyclin E amplification and over expression in clear cell adenocarcinoma of the ovary. *Oncology* 2004; 67(3-4):291-9.
125. Tsuda H, **Birrer MJ**, Ito YM, Ohashi Y, Lin M, Lee C, Wong WH, Rao PH, Lau CC, Berkowitz RS, Wong KK, Mok SC. Identification of DNA copy number changes in microdissected serous ovarian cancer tissue using a cDNA microarray platform *Cancer Genet Cytogenet* 2004 Dec;155(2):97-107.
126. Elam C, Hesson L, Vos MD, Eckfeld K, Ellis C, Bell A, Taylor B S, Krex D, **Birrer MJ**, Latif F,

- and Clark G. RRP22 is a farnesylated, nucleolar, Ras-related protein with tumor suppressor potential. 2005 Cancer Research. Apr 15; 65(8): 3117-25.
127. Leaner VD, Donn timer H, Ellis CA, Clark GJ, and **Birrer MJ**. P75-Ras-GRF1 is a c-Jun/AP-1 target protein: its up regulation results in increased Ras activity and is necessary for c-Jun-induced nonadherent growth of Rat1a cells. Mol Cell Biol. 2005 Apr; 25(8):3324-37.
 128. Katabami M, Donn timer H, Hommura F, Leaner VD, Kinoshita I, and **Birrer MJ**. Cyclin A is a cJun target gene regulated by direct and indirect mechanisms and is necessary for cJun-induced anchorage independent growth in Rat1a cells. J Biol. Chem 2005 Apr 29; 280(17):16728-38.
 129. Jazaeri AA, Awtrey CS, Chandramouli GV, Chuang YE, Khan J, Sotiriou C, Aprelikova O, Yee CJ, Zorn KK, **Birrer MJ**, Barrett JC, Boyd. Gene expression profiles associated with response to chemotherapy in epithelial ovarian cancers. Clin Cancer Res. 2005 Sep 1; 11(17):6300-10.
 130. Zorn KK, Bonome T, Gangi L, Chandramouli GV, Awtrey CS, Gardner GJ, Barrett JC, Boyd J, and **MJ Birrer**. Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. Clin Cancer Res. 2005 Sep 15;11(18):6422-30.
 131. Tsuda H, Ito YM, Ohashi Y, Wong KK, Hashiguchi Y, Welch WR, Berkowitz RS, **Birrer MJ**, and Mok SC. Identification of over expression and amplification of ABCF2 in clear cell ovarian adenocarcinomas by cDNA microarray analyses. Clin Cancer Res. 2005 Oct 1; 11(19 Pt 1):6880-8.
 132. Bonome T, Lee JY, Park DC, Radonovich M, Pise-Masison C, Brady J, Gardner GJ, Hao K, Wong WH, Barrertt JC, Lu KH, Sood AK, Gershenson DM, Mok SC, **Birrer, MJ**. Expression profiling of serous low malignant potential, low-grade, and high-grade tumors of the ovary. Cancer Res. 2005 Nov 15; 65(22):10602-12.
 133. Nummela P, Yin M, Kielosto M, Leaner V, **Birrer MJ**, Holttä E. Thymosin beta4 is a determinant of the transformed phenotype and invasiveness of S-adenosylmethionine decarboxylase-transfected fibroblasts. Cancer Res. 2006 Jan 15; 66(2):701-12.
 134. Wamunyokoli FW, Bonome T, Lee JY, Feltmate CM, Welch WR, Radonovich M, Pise-Masison C, Brady J, Hao K, Berkowitz RS, Mok S, **Birrer MJ**. Expression profiling of mucinous tumors of the ovary identifies genes of clinicopathologic importance. Clin Cancer Res. 2006 Feb 1; 12(3 Pt 1):690-700.
 135. DiFeo A, Narla G, Hirshfeld J, Camacho-Vanegas O, Narla J, Rose SL, Kalir T, Yao S, Levine A, **Birrer MJ**, Bonome T, Friedman SL, Buller RE, Martignetti JA. Roles of KLF6 and KLF6-SV1 in ovarian cancer progression and intraperitoneal dissemination. Clin Cancer Res. 2006 Jun 15; 12(12):3730-9.
 136. **Birrer MJ**. Ovarian cancer: not a borderline issue! Cancer Biol Ther. 2006 Jul; 5(7):786-7.
 137. Sunde JS, Donn timer H, Wu K, Johnson ME, Pestell RG, Rose GS, Mok SC, Brady J, Bonome T, **Birrer MJ**. Expression Profiling Identifies Altered Expression of Genes That Contribute to the

- Inhibition of Transforming Growth Factor- β Signaling in Ovarian Cancer. *Cancer Res.* 2006 Sep 1; 66(17):8404-12.
138. Fountain J, Trimble E, **Birrer MJ**. Summary and discussion of session recommendations. *Gynecol Oncol.* 2006 Nov; 103(2 Suppl. 1):S23-5.
 139. Farley J, Bast RC Jr, **Birrer MJ**. Biomarkers and clinical trial design. *Gynecol Oncol.* 2006 Nov; 3(2 Suppl 1):S3-5.
 140. Farley J, **Birrer MJ**, Christian M.C. The future of phase II trials. *Gynecol Oncol.* 2006 Nov; 103(2 Suppl 1):S20.
 141. Fountain J, Trimble EL, **Birrer MJ**. Introduction. *Gynecol Oncol.* 2006 Nov; 103(2 Suppl 1):S1.
 142. Wu K, Liu M, Li A, Donninger H, Rao M, Jiao X, Lisanti MP, Cvekl A, **Birrer MJ**, Pestell RG. The Cell Fate Determination Factor DACH1 Inhibits c-Jun Induced Contact-Independent Growth. *Mol Biol Cell.* 2007 Mar;18(3):755-67.
 143. Mok SC, Elias KM, Wong KK, Ho K, Bonome T, **Birrer MJ**. Biomarker discovery in epithelial ovarian cancer by genomic approaches. *Adv Cancer Res.* 2007; 96:1-22.
 144. Lu C, Bonome T, Li Y, Kamat AA, Han LY, Schmandt R, Coleman RL, Gershenson DM, Jaffe RB, **Birrer MJ**, Sood AK. Gene alterations identified by expression profiling in tumor-associated endothelial cells from invasive ovarian carcinoma. *Cancer Res.* 2007 Feb 15; 67(4):1757-68.
 145. Wong YF, Cheung TH, Lo KW, Yim SF, Siu NS, Chan SC, Ho TW, Wong KW, Yu MY, Wang VW, Li C, Gardner GJ, Bonome T, Johnson WB, Smith DI, Chung TK, and **Birrer MJ**. Identification of molecular markers and signaling pathway in endometrial cancer in Hong Kong Chinese women by genome-wide gene expression profiling. *Oncogene.* 2007 Mar 22; 26(13):1971-82.
 146. Gershenson DM, **Birrer MJ**. Time for action: a "sea change" in treatment strategies for rare types of epithelial ovarian cancer. *Gynecol Oncol.* 2007 Jul; 106(1):1-3.
 147. **Birrer MJ**, Johnson ME, Hao K, Wong KK, Park DC, Bell A, Welch WR, Berkowitz RS, Mok SC. Whole genome oligonucleotide-based array comparative genomic hybridization analysis identified fibroblast growth factor 1 as a prognostic marker for advanced-stage serous ovarian adenocarcinomas. *J Clin Oncol.* 2007 Jun 1; 25(16):2281-7. Erratum in: *J Clin Oncol.* 2007 Jul 20; 25(21):3184.
 148. Kajanne R, Miettinen P, Mehlem A, Leivonen SK, **Birrer MJ**, Foschi M, Kahari VM, Leppa S. EGF-R regulates MMP function in fibroblasts through MAPK and AP-1 pathways. *J Cell Physiol.* 2007 Aug; 212(2):489-97.
 149. Allen NP, Donninger H, Vos MD, Eckfeld K, Hesson L, Gordon L, **Birrer MJ**, Latif F, Clark GJ. RASSF6 is a novel member of the RASSF family of tumor suppressors. *Oncogene* 2007 Sep

13;26(42):6203-11.

150. Kelloff GJ, Sullivan DC, Baker H, Clarke LP, Nordstrom R, Tatum JL, Dorfman GS, Jacobs P, Berg CD, Pomper MG, **Birrer MJ**, Tempero M, Higley HR, Petty BG, Sigman CC, Maley C, Sharma P, Wax A, Ginsberg GG, Dannenberg AJ, Hawk ET, Messing EM, Grossman HB, Harisinghani M, Bigio IJ, Griebel D, Henson DE, Fabian CJ, Ferrara K, Fantini S, Schnall MD, Zujewski JA, Hayes W, Klein EA, DeMarzo A, Ocak I, Ketterling JA, Tempany C, Shtern F, Parnes HL, Gomez J, Srivastava S, Szabo E, Lam S, Seibel EJ, Massion P, McLennan G, Cleary K, Suh R, Burt RW, Pfeiffer RM, Hoffman JM, Roy HK, Wang T, Limburg PJ, El-Deiry WS, Papadimitrakopoulou V, Hittelman WN, MacAulay C, Veltri RW, Solomon D, Jeronimo J, Richards-Kortum R, Johnson KA, Viner JL, Stratton SP, Rajadhyaksha M, Dhawan A: Workshop Program Committee. Workshop on imaging science development for cancer prevention and preemption. *Cancer Biomarkers*. 2007; 3(1):1-33.
151. Whibley CE, McPhail KL, Keyzers RA, Maritz MF, Leaner VD, **Birrer MJ**, Davies-Coleman MT, Hendricks DT. Reactive oxygen species mediated apoptosis of esophageal cancer cells induced by marine triphenyl toluquinones and oluhydroquinones. *Mol Cancer Ther*. 2007 Sep;6(9):2535-43.
152. Farley J, Ozbun L, Samimi G, **Birrer MJ**. Cell cycle and related proteins. *Dis Markers*. 2007;23(5-6):433-43.
153. Samimi G, Ozbun L, Johnson ME, Mok SC, **Birrer MJ**. Biomarkers of mucinous tumors of the ovary. *Dis Markers*. 2007;23(5-6):389-96.
154. Mok SC, Kwong J, Welch WR, Samimi G, Ozbun L, Bonome T, **Birrer MJ**, Berkowitz RS, Wong KK. Etiology and pathogenesis of epithelial ovarian cancer. *Dis Markers*. 2007;23 (5-6):367-76.
155. Irarrazabal CE, Williams CK, Ely MA, **Birrer MJ**, Garcia-Perez A, Burg MB, Ferraris JD. AP-1 contributes to high NaCl-induced increase in TonEBP/OREBP transactivating activity. *J Biol Chem*. 2008 Feb 1;283(5):2554-63.
156. Landen CN Jr, **Birrer MJ**, Sood AK. Early events in the pathogenesis of epithelial ovarian cancer. *J Clin Oncol*. 2008 Feb 20;26(6):995-1005.
157. Zudaire E, Cuesta N, Murty V, Woodson K, Adams L, Gonzalez N, Martínez A, Narayan G, Kirsch I, Franklin W, Hirsch F, **Birrer MJ**, Cuttitta F. The aryl hydrocarbon receptor repressor is a putative tumor suppressor gene in multiple human cancers. *J Clin Invest*. 2008 Feb;118(2):640-50.
158. Shimizu Y, Kinoshita I, Kikuchi J, Yamazaki K, Nishimura M, **Birrer MJ**, Dosaka-Akita H. Growth inhibition of non-small cell lung cancer cells by AP-1 blockade using a cJun dominant-negative mutant. *Br J Cancer*. 2008 Mar 11;98(5):915-22.
159. Litkouhi B, Fleming E, Welch WR, Berkowitz RS, **Birrer MJ**, Mok SC. Overexpression of CEACAM6 in borderline and invasive mucinous ovarian neoplasms. *Gynecol Oncol*. *Gynecol*

Oncol. 2008 May;109(2):234-9

160. Zhang L, Volinia S, Bonome T, Calin GA, Greshock J, Yang N, Liu CG, Giannakakis A, Alexiou P, Hasegawa K, Johnstone CN, Megraw MS, Adams S, Lassus H, Huang J, Kaur S, Liang S, Sethupathy P, Leminen A, Simossis VA, Sandaltzopoulos R, Naomoto Y, Katsaros D, Gimotty PA, DeMichele A, Huang Q, Bützow R, Rustgi AK, Weber BL, **Birrer MJ**, Hatzigeorgiou AG, Croce CM, Coukos G. Genomic and epigenetic alterations deregulate microRNA expression in human epithelial ovarian cancer. *Proc Natl Acad Sci U S A*. 2008 May 13;105(19):7004-9.
161. Farley J, Ozbun LL, **Birrer MJ**. Genomic analysis of epithelial ovarian cancer. *Cell Res*. 2008 May;18(5):538-48.
162. Stany MP, Bonome T, Wamunyokoli F, Zorn K, Ozbun L, Park DC, Hao K, Boyd J, Sood AK, Gershenson DM, Berkowitz RS, Mok SC, **Birrer MJ**. Classification of ovarian cancer: a genomic analysis. *Adv Exp Med Biol*. 2008;622:23-33.
163. Bonome T, Levine DA, Shih J, Randonovich M, Pise-Masison CA, Bogomolny F, Ozbun L, Brady J, Barrett JC, Boyd J, **Birrer MJ**. A gene signature predicting for survival in suboptimally debulked patients with ovarian cancer. *Cancer Res*. 2008 Jul 1;68(13):5478-86.
164. Sood AK, **Birrer MJ**. Highlights from the 2008 Annual Meeting of the American Association for Cancer Research. *Gynecol Oncol*. 2008 Jul; 110(1):5-6.
165. Park DC, Yeo SG, Wilson MR, Yerbury JJ, Kwong J, Welch WR, Choi YK, **Birrer MJ**, Mok SC, Wong KK. Clusterin interacts with Paclitaxel and confer Paclitaxel resistance in ovarian Cancer. *Neoplasia* 2008 Sep; 10(9):964-72169.
166. Lorenzi PL, Llamas J, Gunsior M, Ozbun L, Reinhold WC, Varma S, Ji H, Kim H, Hutchinson AA, Kohn EC, Goldsmith PK, **Birrer MJ**, Weinstein JN. Asparagine synthetase is a predictive biomarker of L-asparaginase activity in ovarian cancer cell lines. *Mol Cancer Ther* 2008 Oct;7(10):3123-8.
167. Anglesio MS, Arnold JM, George J, Tinker AV, Tothill R, Waddell N, Simms L, Locandro B, Fereday S, Traficante N, Russell P, Sharma R, Birrer MJ; AOCs Study Group, deFazio A, Chenevix-Trench G, Bowtell DD. Mutation of ERBB2 provides a novel alternative mechanism for the ubiquitous ctivation of RAS-MAPK in ovarian serous low malignant potential tumors. *Mol Cancer Res*. 2008 Nov; 6(11): 1678-90.
168. Kikuchi J, Kinoshita I, Shimizu Y, Oizumi S, Nishimura M, **Birrer MJ**, Dosaka-Akita H. Simultaneous blockade of AP-1 and phosphatidylinositol 3-kinase pathway in non-small cell lung cancer cells. *Br J Cancer*. 2008 Dec 16;99(12):2013-9.
169. Arora S, Wang Y, Jia Z, Vardar-Sengul S, Munawar A, Doctor KS, **Birrer MJ**, McClelland M, Adamson E, Mercola D. Egr1 regulates the coordinated expression of numerous EGF receptor target genes as identified by ChIP-on-chip. *Genome Biol*. 2008; 9(11):R166.

170. Callahan MJ, Nagymanyoki Z, Bonome T, Johnson ME, Litkouhi B, Sullivan EH, Hirsch MS, Matulonis UA, Liu J, **Birrer MJ**, Berkowitz RS, Mok SC. Increased HLA-DMB expression in the tumor epithelium is associated with increased CTL infiltration and improved prognosis in advanced-stage serous ovarian cancer. *Cancer Res.* 2008 Dec 1;14(23):7667-73.
171. Leaner VD, Chick JF, Donninger H, Linniola I, Mendoza A, Khanna C, **Birrer MJ**. Inhibition of AP-1 transcriptional activity blocks the migration, invasion, and experimental metastasis of murine osteosarcoma. *Am J Pathol.* 2009 Jan;174(1):265-75.
172. Merritt WM, Lin YG, Han LY, Kamat AA, Spannuth WA, Schmandt R, Urbauer D, Pennacchio LA, Cheng JF, Nick AM, Deavers MT, Mourad-Zeidan A, Wang H, Mueller P, Lenburg ME, Gray JW, Mok S, **Birrer MJ**, Lopez-Berestein G, Coleman RL, Bar-Eli M, Sood AK. Dicer, Drosha, and outcomes in patients with ovarian cancer *N Engl J Med.* 2008 Dec 18;359(25):2641-50.
173. Kitchener HC, Trimble EL, **Birrer MJ**, Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup. Endometrial Cancer State of the Science Meeting. *Int J Gynecol Cancer.* 2009 Jan;19(1):134-40.
174. Chung TK, Cheung TH, Huen NY, Wong KW, Lo KW, Yim SF, Siu NS, Wong YM, Tsang PT, Pang MW, Yu MY, To KF, Mok SC, Wang VW, Li C, Cheung AY, Doran G, **Birrer MJ**, Smith DI, Wong YF. Dysregulated microRNAs and their predicted targets associated with endometrioid endometrial adenocarcinoma in Hong Kong women. *Int J Cancer* 2009 Mar 15; 24(6):1358-65167.
175. Singh S, Manda SM, Sikder D, **Birrer MJ**, Rothermel BA, Garry DJ, Mammen PP. Calcineurin activates cytoglobin transcription in hypoxic myocytes. *J Biol Chem.* 2009 Apr 17;284(16):10409-21.
176. van der Watt PJ, Maske CP, Hendricks DT, Parker MI, Denny L, Govender D, **Birrer MJ**, Leaner VD. The Karyopherin proteins, Crm1 and Karyopherin beta1, are overexpressed in cervical cancer and are critical for cancer cell survival and proliferation. *Int J Cancer.* 2009 Apr 15;124(8):1829-40.
177. Wang B, Khachigian LM, Esau L, **Birrer MJ**, Zhao X, Parker MI, Hendricks DT. A key role for early growth response-1 and nuclear factor-kappaB in mediating and maintaining GRO/CXCR2 proliferative signaling in esophageal cancer. *Mol Cancer Res.* 2009 May;7(5):755-64.
178. Farley J, Fuchiujii S, Darcy KM, Tian C, Hoskins WJ, McGuire WP, Hanjani P, Warshal D, Greer BE, Belinson J, **Birrer MJ**. Associations between ERBB2 amplification and progression-free survival and overall survival in advanced stage, suboptimally-resected epithelial ovarian cancers: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 2009 Jun;113(3):341-7.
179. Nosov V, Su F, Amneus M, **Birrer MJ**, Robins T, Kotlerman J, Reddy S, Farias-Eisner R. Validation of serum biomarkers for detection of early-stage ovarian cancer. *Am J Obstet Gynecol.* 2009 Jun;200(6):639.e1-5.

180. Calvisi DF, Donniger H, Vos MD, **Birrer MJ**, Gordon L, Leaner V, Clark GJ. NORE1A tumor suppressor candidate modulates p21CIP1 via p53. *Cancer Res.* 2009 Jun 1;69(11):4629-37. Epub 2009 May 12
181. Kwong J, Chan FL, Wong KK, **Birrer MJ**, Archibald KM, Balkwill FR, Berkowitz RS, Mok SC. Inflammatory cytokine tumor necrosis factor alpha confers precancerous phenotype in an organoid model of normal human ovarian surface epithelial cells. *Neoplasia*. 2009 Jun;11(6):529-41.
182. Terry KL, Vitonis AF, Hernandez D, Lurie G, Song H, Ramus SJ, Titus-Ernstoff L, Carney ME, Wilkens LR, Gentry-Maharaj A, Menon U, Gayther SA, Pharaoh PD, Goodman MT, Cramer DW, **Birrer MJ**. A polymorphism in the GALNT2 gene and ovarian cancer risk in four population based case-control studies. *Int J Mol Epidemiol Genet*. 2010 Jul 26;1(4):272-7
183. Demelash A, Kim H, Jensen-Taubman S, Dakir EH, Ozbun L, **Birrer MJ**, Linnoila, RI. Matrilysin-1 Mediates Bronchiolization of Alveoli, A Potential Premalignant Change in Lung Cancer. *J Pathol*. 2009 Aug;175(2):592-604.
184. Wang XY, Demelash A, Kim H, Jensen-Taubman S, Dakir el H, Ozbun L, **Birrer MJ**, Linnoila RI. Matrilysin-1 mediates bronchiolization of alveoli, a potential premalignant change in lung cancer. *Am J Pathol*. 2009 Aug;175(2):592-604.
185. Darcy KM, Brady WE, Blacato JK, Dickson RB, Hoskins WJ, McGuire WP, **Birrer MJ**. Prognostic relevance of c-MYC gene amplification and polysomy for chromosome 8 in suboptimally-resected, advanced stage epithelial ovarian cancers: A Gynecologic Oncology Group study. *Gynecol Oncol*. 2009 Sep;114(3):472-9.
186. Farley JH, Tian C, Rose GS, Brown CL, **Birrer MJ**, Maxwell GL. Race does not impact outcome for advanced ovarian cancer patients treated with cisplatin/paclitaxel: an analysis of Gynecologic Oncology Group trials. *Cancer*. 2009 Sep 15;115(18):4210-7.
187. Farley J, **Birrer MJ**. Novel Therapeutic Targets, *Cancer Treat Res*. 2009;149:63-84.
188. Mok SC, Bonome T, Vathipadiekal V, Bell A, Johnson ME, Wong KK, Park DC, Hao K, Yip DK, Donniger H, Ozbun L, Samimi G, Brady J, Randonovich M, Pise-Masison CA, Barrett JC, Wong WH, Welch WR, Berkowitz RS, **Birrer MJ**. A gene signature predictive for outcome in advanced ovarian cancer identifies a survival factor: microfibril-associated glycoprotein 2. *Cancer Cell*. 2009 Dec 8;16(6):521-32.
189. Na YJ, Farley J, Zeh A, del Carmen M, Penson R, **Birrer MJ**. Ovarian cancer: markers of response. *Int J Gynecol Cancer*. 2009 Dec;19 Suppl 2:S21-9.
190. Farley JH, Tian C, Rose GS, Brown CL, **Birrer MJ**, Risinger JI, Thigpen JT, Fleming GF, Gallion HH, Maxwell GL. Chemotherapy intensity and toxicity among black and white women with advanced and Recurrent endometrial cancer: A Gynecologic Oncology Group Study. *Cancer*. 2010;Jan 15;116(2):355-61.

191. Minig L, Trimble EL, **Birrer MJ**, Kim KY, Takebe N, Abrams JS. NIH and NCI support for development of novel therapeutics in gynecologic cancer: a user's guide *Gynecol Oncol*. 2010 Feb;116(2):177-80.
192. Clauss A, Ng V, Liu J, Piao H, Russo M, Vena N, Sheng Q, Hirsch MS, Bonome T, Matulonis U, Ligon AH, **Birrer MJ**, Drapkin R. Overexpression of elafin in ovarian carcinoma is driven by genomic gains and activation of the nuclear factor kappaB pathway and is associated with poor overall survival. *Neoplasia*. 2010 Feb;12(2):161-72.
193. Byron SA, Gartside MG, Wellens CL, Goodfellow PJ, **Birrer MJ**, Campbell IG, Pollock PM. FGFR2 mutations are rare across histologic subtypes of ovarian cancer. *Gynecol Oncol*. 2010 Apr;117(1):125-9.
194. Huh WK, Sill MW, Darcy KM, Elias KM, Hoffman JS, Boggess JF, Alvarez RD, Long HJ, O'Malley DM, **Birrer MJ**. Efficacy and safety of imatinib mesylate (Gleevec) and immunohistochemical expression of c-Kit and PDGFR-beta in a Gynecologic Oncology Group Phase II Trial in women with recurrent or persistent carcinosarcomas of the uterus. *Gynecol Oncol*. 2010 May;117(2):248-54.
195. Hernandez L, Hsu SC, Davidson B, **Birrer MJ**, Kohn EC, Annunziata CM. Activation of NF-kappaB signaling by inhibitor of NF-kappaB kinase beta increases aggressiveness of ovarian cancer. *Cancer Res*. 2010 May 15;70(10):4005-14.
196. Darcy KM, **Birrer MJ**. Translational research in the Gynecologic Oncology Group: evaluation of ovarian cancer markers, profiles, and novel therapies. *Gynecol Oncol*. 2010 Jun;117(3):429-39.
197. Annunziata CM, Stavnes HT, Kleinberg L, Berner A, Hernandez LF, **Birrer MJ**, Steinberg SM, Davidson B, Kohn EC. Nuclear factor kappaB signaling by inhibitor NF-kappa beta increases aggressiveness of ovarian cancer. *Cancer*. 2010 Jul 1;116(13):3276-84.
198. Annunziata, CM **Birrer MJ**. CD157 in ovarian carcinoma: How does it help us? *J Natl Cancer Inst*. 2010 Aug 4;102(15):1104-5.
199. Lu C, Han HD, Mangala LS, Ali-Fehmi R, Newton CS, Ozbun L, Armaiz-Pena GN, Hu W, Stone RL, Munkarah A, Ravoori MK, Shahzad MM, Lee JW, Mora E, Langley RR, Carroll AR, Matsuo K, Spannuth WA, Schmandt R, Jennings NB, Goodman BW, Jaffe RB, Nick AM, Kim HS, Guven EO, Chen YH, Li LY, Hsu MC, Coleman RL, Calin GA, Denkbass EB, Lim JY, Lee JS, Kundra V, **Birrer MJ**, Hung MC, Lopez-Berestein G, Sood AK. Regulation of tumor angiogenesis by EZH2 *Cancer Cell*. 2010 Aug 9;18(2):185-97.
200. Kikuchi J, Kinoshita I, Shimizu Y, Kikuchi E, Takeda K, Aburatani H, Oizumi S, Konishi J, Kaga K, Matsuno Y, **Birrer MJ**, Nishimura M, Dosaka-Akita H. Minichromosome maintenance (MCM) protein 4 as a marker for proliferation and its clinical and clinicopathological significance in non-small cell lung cancer. *Lung Cancer*. 2011 May;72(2):229-37.
201. Ghosh S, Albitar L, Lebaron R, Welch WR, Samimi G, **Birrer MJ**, Berkowitz RS, Mok SC. Up-

regulation of stromal versican expression in advanced state serous ovarian cancer. *Gynecol Oncol.* 2010 Oct;119(1):114-20.

202. Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, Widschwendter M, Vierkant RA, Larson MC, Kjaer SK, **Birrer MJ**, Berchuck A, Schildkraut J, Tomlinson I, Kiemeny LA, Cook LS, Gronwald J, Garcia-Closas M, Gore ME, Campbell I, Whittemore AS, Sutphen R, Phelan C, Anton-Culver H, Pearce CL, Lambrechts D, Rossing MA, Chang-Claude J, Moysich KB, Goodman MT, Dörk T, Nevanlinna H, Ness RB, Rafnar T, Hogdall C, Hogdall E, Fridley BL, Cunningham JM, Sieh W, McGuire V, Godwin AK, Cramer DW, Hernandez D, Levine D, Lu K, Iversen ES, Palmieri RT, Houlston R, van Altena AM, Aben KK, Massuger LF, Brooks-Wilson A, Kelemen LE, Le ND, Jakubowska A, Lubinski J, Medrek K, Stafford A, Easton DF, Tyrer J, Bolton KL, Harrington P, Eccles D, Chen A, Molina AN, Davila BN, Arango H, Tsai YY, Chen Z, Risch HA, McLaughlin J, Narod SA, Ziogas A, Brewster W, Gentry-Maharaj A, Menon U, Wu AH, Stram DO, Pike MC; Wellcome Trust Case-Control Consortium, Beesley J, Webb PM; Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium (OCAC). A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. *Nat Genet.* 2010 Oct;42(10):874-9.
203. Bolton KL, Tyrer J, Song H, Ramus SJ, Notaridou M, Jones C, Sher T, Gentry-Maharaj A, Wozniak E, Tsai YY, Weidhaas J, Paik D, Van Den Berg DJ, Stram DO, Pearce CL, Wu AH, Brewster W, Anton-Culver H, Ziogas A, Narod SA, Levine DA, Kaye SB, Brown R, Paul J, Flanagan J, Sieh W, McGuire V, Whittemore AS, Campbell I, Gore ME, Lissowska J, Yang HP, Medrek K, Gronwald J, Lubinski J, Jakubowska A, Le ND, Cook LS, Kelemen LE, Brook-Wilson A, Massuger LF, Kiemeny LA, Aben KK, van Altena AM, Houlston R, Tomlinson I, Palmieri RT, Moorman PG, Schildkraut J, Iversen ES, Phelan C, Vierkant RA, Cunningham JM, Goode EL, Fridley BL, Kruger-Kjaer S, Blacker J, Hogdall E, Hogdall C, Gross J, Karlan BY, Ness RB, Edwards RP, Odunsi K, Moyisch KB, Baker JA, Modugno F, Heikkinen T, Butzow R, Nevanlinna H, Leminen A, Bogdanova N, Antonenkova N, Doerk T, Hillemanns P, Dürst M, Runnebaum I, Thompson PJ, Carney ME, Goodman MT, Lurie G, Wang-Gohrke S, Hein R, Chang-Claude J, Rossing MA, Cushing-Haugen KL, Doherty J, Chen C, Rafnar T, Besenbacher S, Sulem P, Stefansson K, **Birrer MJ**, Terry KL, Hernandez D, Cramer DW, Vergote I, Amant F, Lambrechts D, Despierre E, Fasching PA, Beckmann MW, Thiel FC, Ekici AB, Chen X; Australian Ovarian Cancer Study Group; Australian Cancer Study (Ovarian Cancer); Ovarian Cancer Association Consortium, Johnatty SE, Webb PM, Beesley J, Chanock S, Garcia-Closas M, Sellers T, Easton DF, Berchuck A, Chenevix-Trench G, Pharoah PD, Gayther SA. Common variants at 19p13 are associated with susceptibility to ovarian cancer. *Nat Genet.* 2010 Oct;42(10):880-4.
204. **Birrer MJ**. The origin of ovarian cancer—is it getting clearer? *N Engl J Med.* 2010 Oct 14;363(16):1574-5.
205. Trimble EL, **Birrer MJ**, Hoskins WJ, Marth C, Petryshyn R, Quinn M, Thomas GM, Kitchener HC. Current academic clinical trials in ovarian cancer: Gynecologic Cancer Intergroup (GCIG) and United States National Cancer Institute (NCI) clinical trials planning meeting, May, 2009. *Int J Gynecol Cancer.* 2010 Oct;20(7):1290-8.
206. Matei D, Sill MW, Lankes HA, Degeest K, Bristow RE, Mutch D, Yamada SD, Cohn D, Calvert V,

- Farley J, Petricoin EF, **Birrer MJ**. Activity of Sorafenib in Recurrent Ovarian Cancer and Primary Peritoneal Carcinomatosis: A Gynecologic Oncology Group Trial. *Clin Oncol*. 2011 Jan 1;29(1):69-75.
207. Emmanuel C, Gava N, Kennedy C, Balleine RL, Sharma R, Wain G, Brand A, Hogg R, Etemadmoghadam D, George J; Australian Ovarian Cancer Study Group, **Birrer MJ**, Clarke CL, Chenevix-Trench G, Bowtell DD, Harnett PR, deFazio A. Comparison of expression profiles in ovarian epithelium in vivo and ovarian cancer identifies novel candidate genes involved in disease pathogenesis. *PLoS One*. 2011 Mar 15;6(3):e17617.
208. Konstantinopoulos PA, Cannistra SA, Fountzilias H, Culhane A, Pillay K, Rueda B, Cramer D, Seiden M, **Birrer M**, Coukos G, Zhang L, Quackenbush J, Spentzos D. Integrated analysis of multiple microarray datasets identifies a reproducible survival predictor in ovarian cancer. *PLoS One*. 2011 Mar 29;6(3):e18202.
209. Helland A, Anglesio MS, George J, Cowin PA, Johnstone CN, House CM, Sheppard KE, Etemadmoghadam D, Melnyk N, Rustgi AK, Phillips WA, Johnsen H, Holm R, Kristensen GB, **Birrer MJ**, Australian Ovarian Cancer Study Group, Pearson RB, Børresen-Dale AL, Huntsman DG, Defazio A, Creighton CJ, Smyth GK, Bowtell DD. Deregulation of MYCN, LIN28B and LET7 in a Molecular Subtype of Aggressive High-Grade Serous Ovarian Cancers. *PLoS One*. 2011 Apr 13;6(4):e18064.
210. Anglesio MS, George J, Kulbe H, Friedlander M, Rischin D, Lemech C, Power J, Coward J, Cowin PA, House CM, Chakravarty P, Gorringer KL, Campbell IG; Australian Ovarian Cancer Study Group, Okamoto A, **Birrer MJ**, Huntsman DG, de Fazio A, Kalloger SE, Balkwill F, Gilks CB, Bowtell DD. IL6-STAT3-HIF signaling and therapeutic response to the angiogenesis inhibitor sunitinib in ovarian clear cell cancer. *Clin Cancer Res*. 2011 Apr 15;17(8):2538-48.
211. Ledermann JA, Marth C, Carey MS, **Birrer M**, Bowtell DD, Kaye S, McNeish I, Oza A, Scambia G, Rustin G, Stehman FB, Gershenson D, Thomas G, Berns E, Casado A, Ottevanger N, Hilpert F, Kim BG, Okamoto A, Bacon M, Kitchener H, Stuart GC; and on behalf of the Gynecologic Cancer InterGroup. Role of molecular agents and targeted therapy in clinical trials for women with ovarian cancer. *Int J Gynecol Cancer*. 2011 May 21(4):763-70.
212. Maritz MF, van der Watt PJ, Holderness N, **Birrer MJ**, Leaner VD. Inhibition of AP-1 suppresses cervical cancer cell proliferation and is associated with p21 expression. *Biol Chem*. 2011 May 392(5):439-48.
213. Kikuchi J, Kinoshita I, Shimizu Y, Kikuchi E, Takeda K, Aburatani H, Oizumi S, Konishi J, Kaga K, Matsuno Y, **Birrer MJ**, Nishimura M, Dosaka-Akita H. Minichromosome maintenance (MCM) protein 4 as a marker for proliferation and its clinical and clinicopathological significance in non-small cell lung cancer. *Lung Cancer*. 2011 May 72(2):229-37.
214. Farley J, Sill MW, **Birrer M**, Walker J, Schilder RJ, Thigpen JT, Coleman RL, Miller E, Rose PG, Lankes HA. Phase II study of cisplatin plus cetuximab in advanced, recurrent, and previously treated cancers of the cervix and evaluation of epidermal growth factor receptor

immunohistochemical expression: A Gynecologic Oncology Group study. *Gynecol Oncol.* 2011 May 1 121(2):303-8.

215. Farley J, Smith LM, Darcy KM, Brady MF, Bell J, McGuire W, **Birrer MJ**. Nuclear P27 expression in benign, borderline (LMP) and invasive tumors of the ovary and its association with prognosis: A gynecologic oncology group study. *Gynecol Oncol.* 2011 May 1;121(2):395-401.
216. King ER, Tung CS, Tsang YT, Zu Z, Lok GT, Deavers MT, Malpica A, Wolf JK, Lu KH, **Birrer MJ**, Mok SC, Gershenson DM, Wong KK. The Anterior Gradient Homolog 3 (AGR3) Gene Is Associated With Differentiation and Survival in Ovarian Cancer. *Am J Surg Pathol.* 2011 Jun;35(6):904-12.
217. Pharoah PD, Palmieri RT, Ramus SJ, Gayther SA, Andrulis IL, Anton-Culver H, Antonenkova N, Antoniou AC, Goldgar D; for the BCFR Investigators, Beattie MS, Beckmann MW, **Birrer MJ**, Bogdanova N, Bolton KL, Brewster W, Brooks-Wilson A, Brown R, Butzow R, Caldes T, Caligo MA, Campbell I, Chang-Claude J, Chen YA, Cook LS, Couch FJ, Cramer DW, Cunningham JM, Despiere E, Doherty JA, Dörk T, Dürst M, Eccles DM, Ekici AB, Easton D; for the EMBRACE Investigators, Fasching PA, de Fazio A, Fenstermacher DA, Flanagan JM, Fridley BL, Friedman E, Gao B, Sinilnikova O; for the GEMO Study Collaborators, Gentry-Maharaj A, Godwin AK, Goode EL, Goodman MT, Gross J, Hansen TV, Harnett P, Rookus M; for the HEBON Investigators, Heikkinen T, Hein R, Høgdall C, Høgdall E, Iversen ES, Jakubowska A, Johnatty SE, Karlan BY, Kauff ND, Kaye SB, Chenevix-Trench G; for the kConFab Investigators and the Consortium of Investigators of Modifiers of BRCA1/2, Kelemen LE, Kiemeny LA, Kjaer SK, Lambrechts D, Lapolla JP, Lázaro C, Le ND, Leminen A, Leunen K, Levine DA, Lu Y, Lundvall L, Macgregor S, Marees T, Massuger LF, McLaughlin JR, Menon U, Montagna M, Moysich KB, Narod SA, Nathanson KL, Nedergaard L, Ness RB, Nevanlinna H, Nickels S, Osorio A, Paul J, Pearce CL, Phelan CM, Pike MC, Radice P, Rossing MA, Schildkraut JM, Sellers TA, Singer CF, Song H, Stram DO, Sutphen R, Lindblom A; for the SWE-BRCA Investigators, Terry KL, Tsai YY, van Altena AM, Vergote I, Vierkant RA, Vitonis AF, Walsh C, Wang-Gohrke S, Wappenschmidt B, Wu AH, Ziogas A, Berchuck A, Risch HA; for the Ovarian Cancer Association Consortium. The Role of KRAS rs61764370 in Invasive Epithelial Ovarian Cancer: Implications for Clinical Testing. *Clin Cancer Res.* 2011 Jun 1;17(11):3742-3750.
218. Permuth-Wey J, Kim D, Tsai YY, Lin HY, Chen YA, Barnholtz-Sloan J, **Birrer MJ**, Bloom G, Chanock SJ, Chen Z, Cramer DW, Cunningham JM, Dagne G, Ebbert-Syrett J, Fenstermacher D, Fridley BL, Garcia-Closas M, Gayther SA, Ge W, Gentry-Maharaj A, Gonzalez-Bosquet J, Goode EL, Iversen E, Jim H, Kong W, McLaughlin J, Menon U, Monteiro AN, Narod SA, Pharoah PD, Phelan CM, Qu X, Ramus SJ, Risch H, Schildkraut JM, Song H, Stockwell H, Sutphen R, Terry KL, Tyrer J, Vierkant RA, Wentzensen N, Lancaster JM, Cheng JQ, Sellers TA; Ovarian Cancer Association Consortium. LIN28B polymorphisms influence susceptibility to epithelial ovarian cancer. *Cancer Res.* 2011 Jun 1;71(11):3896-903.
219. Bodurka DC, Deavers MT, Tian C, Sun CC, Malpica A, Coleman RL, Lu KH, Sood AK, **Birrer MJ**, Ozols R, Baergen R, Emerson RE, Steinhoff M, Behmaram B, Rasty G, Gershenson DM. Reclassification of serous ovarian carcinoma by a 2-tier system: A Gynecologic Oncology Group Study. *Cancer.* 2012 Jun 15;118(12):3087-94.

220. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011 Jun 29;474(7353):609-15.
221. Stany MP, Vathipadiekal V, Ozbun L, Stone RL, Mok SC, Xue H, Kagami T, Wang Y, McAlpine JN, Bowtell D, Gout PW, Miller DM, Gilks CB, Huntsman DG, Ellard SL, Wang YZ, Vivas-Mejia P, Lopez-Berestein G, Sood AK, **Birrer MJ**. Identification of novel therapeutic targets in microdissected clear cell ovarian cancers. *PLoS One*. 2011;6(7):e21121
222. Righi E, Kashiwagi S, Yuan J, Santosuosso M, Leblanc P, Ingraham R, Forbes B, Edelblute B, Collette B, Xing D, Kowalski M, Mingari MC, Vianello F, **Birrer MJ**, Orsulic S, Dranoff G, Poznansky M. CXCL12/CXCR4 blockade induces multimodal anti-tumor effects and prolongs survival of immune competent mice with ovarian cancer. *Cancer Res*. 2011 Aug 15;71(16):5522-5534.
223. Hagemann AR, Cadungog M, Hagemann IS, Hammond R, Adams SF, Chu CS, Rubin S, Zhang L, Addya K, **Birrer MJ**, Gimotty PA, Coukos G. Tissue-based immune monitoring I: Tumor core needle biopsies allow in-depth interrogation of the tumor microenvironment. *Cancer Biol Ther*. 2011 Aug 15;12(4):357-66.
224. Hagemann AR, Hagemann IS, Cadungog M, Hwang WT, Patel P, Lal P, Hammond R, Gimotty PA, Chu CS, Rubin S, **Birrer MJ**, Powell DJ Jr, Feldman MD, Coukos G. Tissue-based immune monitoring II: Multiple tumor sites reveal immunologic homogeneity in serous ovarian carcinoma. *Cancer Biol Ther*. 2011 Aug 15;12(4):367-77.
225. Permeth-Wey J, Chen Z, Tsai YY, Lin HY, Chen YA, Barnholtz-Sloan J, **Birrer MJ**, Chanock SJ, Cramer DW, Cunningham JM, Fenstermacher D, Fridley BL, Garcia-Closas M, Gayther SA, Gentry-Maharaj A, Gonzalez Bosquet J, Iversen E, Jim H, McLaughlin J, Menon U, Narod SA, Phelan CM, Ramus SJ, Risch H, Song H, Sutphen R, Terry KL, Tyrer J, Vierkant RA, Wentzensen N, Lancaster JM, Cheng JQ, Berchuck A, Pharoah PD, Schildkraut JM, Goode EL, Sellers TA. MicroRNA processing and binding site polymorphisms are not replicated in the Ovarian Cancer Association Consortium. *Cancer Epidemiol Biomarkers Prev*. 2011 Aug;20(8):1793-1797.
226. Bitler BG, Nicodemus JP, Li H, Cai Q, Wu H, Hua X, Li T, **Birrer MJ**, Godwin AK, Cairns P, Zhang R. Wnt5a Suppresses Epithelial Ovarian Cancer by Promoting Cellular Senescence. *Cancer Res*. 2011 Oct 1;71(19):6184-94.
227. McCann CK, Growdon WB, Kulkarni-Datar K, Curley MD, Friel AM, Proctor JL, Sheikh H, Deyneko I, Ferguson JA, Vathipadiekal V, **Birrer MJ**, Borger DR, Mohapatra G, Zukerberg LR, Foster R, Macdougall JR, Rueda BR. Inhibition of hedgehog signaling antagonizes serous ovarian cancer growth in a primary xenograft model. *PLoS One*. 2011;6(11):e28077.
228. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, **Birrer MJ**, Liang SX; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011 Dec

29;365(26):2473-83.

229. Vathipadiekal V, Saxena D, Mok SC, Hauschka PV, Ozbun L, **Birrer MJ**. Identification of a potential ovarian cancer stem cell gene expression profile from advanced stage papillary serous ovarian cancer. *PLoS One*. 2012;7(1):e29079.
230. White KL, Schildkraut JM, Palmieri RT, Iversen ES, Berchuck A, Vierkant RA, Rider DN, Charbonneau B, Cicek MS, Sutphen R, **Birrer MJ**, Pharoah PD, Song H, Tyrer J, Gayther SA, Ramus SJ, Wentzensen N, Yang HP, Garcia-Closas M, Phelan CM, Cunningham JM, Fridley BL, Sellers TA, Goode EL. Ovarian Cancer Risk Associated with Inherited Inflammation-Related Variants. *Cancer Res*. 2012 Mar 1;72(5):1064-1069.
231. Li H, Bitler BG, Vathipadiekal V, Maradeo ME, Slifker M, Creasy CL, Tummino PJ, Cairns P, **Birrer MJ**, Zhang R. ALDH1A1 Is a Novel EZH2 Target Gene in Epithelial Ovarian Cancer Identified by Genome-Wide Approaches. *Cancer Prev Res (Phila)*. 2012 Mar;5(3):484-91.
232. Stevens KN, Kelemen LE, Wang X, Fridley BL, Vierkant RA, Fredericksen Z, Armasu SM, Tsai YY, Berchuck A, Association Consortium OC, Narod SA, Phelan CM, Sutphen R, **Birrer MJ**, Schildkraut JM, Sellers TA, Goode EL, Couch FJ. Common variation in Nemo-like kinase (NLK) is associated with risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2012 Mar;21(3):523-528.
233. Del Carmen MG, **Birrer M**, Schorge JO. Carcinosarcoma of the ovary: A review of the literature. *Gynecol Oncol*. 2012 Apr;125(1):271-7.
234. Ferriss JS, Kim Y, Duska L, **Birrer M**, Levine DA, Moskaluk C, Theodorescu D, Lee JK. Multi-gene expression predictors of single drug responses to adjuvant chemotherapy in ovarian carcinoma: predicting platinum resistance. *PLoS One*. 2012;7(2):e30550.
235. Engler DA, Gupta S, Growdon WB, Drapkin RI, Nitta M, Sergent PA, Allred SF, Gross J, Deavers MT, Kuo WL, Karlan BY, Rueda BR, Orsulic S, Gershenson DM, **Birrer MJ**, Gray JW, Mohapatra G. Genome wide DNA copy number analysis of serous type ovarian carcinomas identifies genetic markers predictive of clinical outcome. *PLoS One*. 2012;7(2):e30996.
236. Kassler S, Donniger H, **Birrer MJ**, Clark GJ. RASSF1A and the Taxol Response in Ovarian Cancer. *Mol Bio Int*. 2012;263267.
237. Rubatt JM, Darcy KM, Tian C, Muggia F, Dhir R, Armstrong DK, Bookman MA, Niedernhofer LJ, Deloia J, **Birrer M**, Krivak TC. Pre-treatment tumor expression of ERCC1 in women with advanced stage epithelial ovarian cancer is not predictive of clinical outcomes: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012 May;125(2):421-6.
238. Alsop K, Fereday S, Meldrum C, Defazio A, Emmanuel C, George J, Dobrovic A, **Birrer MJ**, Webb PM, Stewart C, Friedlander M, Fox S, Bowtell D, Mitchell G. BRCA Mutation Frequency and Patterns of Treatment Response in BRCA Mutation-Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group. *J Clin Oncol*. 2012 Jul 20;30(21):2654-

63.

239. Del Carmen MG, **Birrer M**, Schorge JO. Clear cell carcinoma of the ovary: A review of the literature. *Gynecol Oncol.* 2012 Sep;126(3):481-90.
240. Del Carmen MG, **Birrer M**, Schorge JO. Uterine papillary serous cancer: A review of the literature. *Gynecol Oncol.* 2012 Dec; 127(3):651-61.
241. Sethi G, Pathak HB, Zhang H, Zhou Y, Einarson MB, Vathipadiekal V, Gunewardena S, **Birrer MJ**, Godwin AK. An RNA interference lethality screen of the human druggable genome to identify molecular vulnerabilities in epithelial ovarian cancer. *PLoS One.* 2012;7(10):e47086. doi: 10.1371/journal.pone.0047086. Epub 2012 Oct 9.
242. Li H, Cai Q, Wu H, Vathipadiekal V, Dobbin ZC, Li T, Hua X, Landen CN Jr, **Birrer MJ**, Sanchez-Beato M, Zhang R. SUZ12 promotes human epithelial ovarian cancer by suppressing apoptosis via silencing HRK. *Mol Cancer Res.* 2012 Nov; 10 (11): 1462-72
243. May T, Shoni M, Crum CP, Xian W, Vathipadiekal V, **Birrer M**, Rosen B, Tone A, Murphy KJ. Low-grade and high-grade serous Mullerian carcinoma: Review and analysis of publicly available gene expression profiles. *Gynecol Oncol.* 2012 Dec 16. S0090-8258(12)00956-0. 10.1016/j.ygyno.2012.12.009.
244. Verhaak RG, Tamayo P, Yang JY, Hubbard D, Zhang H, Creighton CJ, Feraday S, Lawrence M, Carter SL, Mermel CH, Kostic AD, Etemadmoghadam D, Saksena G, Cibulskis K, Duraisamy S, Levanon K, Sougnez C, Tsherniak A, Gomez S, Onofrio R, Gabriel S, Chin L, Zhang N, Spellman PT, Zhang Y, Akbani R, Hoadley KA, Kahn A, Köbel M, Huntsman D, Soslow RA, Defazio A, **Birrer MJ**, Gray JW, Weinstein JN, Bowtell DD, Drapkin R, Mesirov JP, Getz G, Levine DA, Meyerson M. Prognostically relevant gene signatures of high-grade serous ovarian carcinoma. *J Clin Invest.* 2013 Jan 2;123(1):517-25.
245. Zaid T, Yeung TL, Thompson MS, Leung C, Harding T, Co N, Schmandt RE, Kwan SY, Rodriguez-Aguayo C, Lopez-Berestein G, Sood AK, Wong KK, **Birrer MJ**, Mok SC Identification of FGFR4 as a Potential Therapeutic Target for Advanced-Stage High-grade Serous Ovarian Cancer. *Clin Cancer Res.* 2013 Jan 29.
246. Farley J, Brady WE, Vathipadiekal V, Lankes HA, Coleman R, Morgan MA, Mannel R, Yamada SD, Mutch D, Rodgers WH, **Birrer M**, Gershenson DM Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. *Lancet Oncol.* 2013 Feb;14(2):134-140.
247. Permuth-Wey J, Lawrenson K, Shen HC, Velkova A, Tyrer JP, Chen Z, Lin HY, Ann Chen Y, Tsai YY, Qu X, Ramus SJ, Karevan R, Lee J, Lee N, Larson MC, Aben KK, Anton-Culver H, Antonenkova N, Antoniou AC, Armasu SM; stralian Cancer Study; stralian Ovarian Cancer Study, Bacot F, Baglietto L, Bandera EV, Barnholtz-Sloan J, Beckmann MW, **Birrer MJ**, Bloom G, Bogdanova N, Brinton LA, Brooks-Wilson A, Brown R, Butzow R, Cai Q, Campbell I, Chang-Claude J, Chanock S, Chenevix-Trench G, Cheng JQ, Cicek MS, Coetzee GA; Consortium of

- Investigators of Modifiers of BRCA1/2, Cook LS, Couch FJ, Cramer DW, Cunningham JM, Dansonka-Mieszkowska A, Despierre E, Doherty JA, Dörk T, du Bois A, Dürst M, Easton DF, Eccles D, Edwards R, Ekici AB, Fasching PA, Fenstermacher DA, Flanagan JM, Garcia-Closas M, Gentry-Maharaj A, Giles GG, Glasspool RM, Gonzalez-Bosquet J, Goodman MT, Gore M, Górski B, Gronwald J, Hall P, Halle MK, Harter P, Heitz F, Hillemanns P, Hoatlin M, Høgdall CK, Høgdall E, Hosono S, Jakubowska A, Jensen A, Jim H, Kalli KR, Karlan BY, aye SB, Kelemen LE, Kiemeny LA, Kikkawa F, Konecny GE, Krakstad C, Krüger Kjaer S, Kupryjanczyk J, Lambrechts D, Lambrechts S, Lancaster JM, Le ND, Leminen A, Levine DA, Liang D, Kiong Lim B, Lin J, Lissowska J, Lu KH, Lubiński J, Lurie G, Massuger LF, Matsuo K, McGuire V, McLaughlin JR, Menon U, Modugno F, Moysich KB, Nakanishi T, Narod SA, Nedergaard L, Ness RB, Nevanlinna H, Nickels S, Noushmehr H, Odunsi K, Olson SH, Orlov I, Paul J, Pearce CL, Pejovic T, Pelttari LM, Pike MC, Poole EM, Raska P, Renner SP, Risch HA, Rodriguez-Rodriguez L, Anne Rossing M, Rudolph A, Runnebaum IB, Rzepecka IK, Salvesen HB, Schwaab I, Severi G, Shridhar V, Shu XO, Shvetsov YB, Sieh W, Song H, Southey MC, Spiewankiewicz B, Stram D, Sutphen R, Teo SH, Terry KL, Tessier DC, Thompson PJ, Tworoger SS, van Altena AM, Vergote I, Vierkant RA, Vincent D, Vitonis AF, Wang-Gohrke S, Palmieri Weber R, Wentzensen N, Whittemore AS, Wik E, Wilkens LR, Winterhoff B, Ling Woo Y, Wu AH, Xiang YB, Yang HP, Zheng W, Ziogas A, Zulkifli F, Phelan CM, Iversen E, Schildkraut JM, Berchuck A, Fridley BL, Goode EL, Pharoah PD, Monteiro AN, Sellers TA, Gayther SA. Identification and molecular characterization of a new ovarian cancer susceptibility locus at 17q21.31. *Nat Commun.* 2013 Mar 27;4:1627
248. Ganzfried BF, Riester M, Haibe-Kains B, Risch T, Tyekucheva S, Jazic I, Wang XV, Ahmadifar M, **Birrer MJ**, Parmigiani G, Huttenhower C, Waldron L. CuratedOvarianData: Clinically annotated data for the ovarian cancer transcriptome. *Database (Oxford).* 2013 Apr 2;2013
249. Pharoah PD, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, Buckley M, Fridley BL, Tyrer JP, Shen H, Weber R, Karevan R, Larson MC, Song H, Tessier DC, Bacot F, Vincent D, Cunningham JM, Dennis J, Dicks E; stralian Cancer Study; stralian Ovarian Cancer Study Group, Aben KK, Anton-Culver H, Antonenkova N, Armasu SM, Baglietto L, Bandera EV, Beckmann MW, **Birrer MJ**, Bloom G, Bogdanova N, Brenton JD, Brinton LA, Brooks-Wilson A, Brown R, Butzow R, Campbell I, Carney ME, Carvalho RS, Chang-Claude J, Chen YA, Chen Z, Chow WH, Cicek MS, Coetzee G, Cook LS, Cramer DW, Cybulski C, Dansonka-Mieszkowska A, Despierre E, Doherty JA, Dörk T, du Bois A, Dürst M, Eccles D, Edwards R, Ekici AB, Fasching PA, Fenstermacher D, Flanagan J, Gao YT, Garcia-Closas M, Gentry-Maharaj A, Giles G, Gjyshi A, Gore M, Gronwald J, Guo Q, Halle MK, Harter P, Hein A, Heitz F, Hillemanns P, Hoatlin M, Høgdall E, Høgdall CK, Hosono S, Jakubowska A, Jensen A, Kalli KR, Karlan BY, Kelemen LE, Kiemeny LA, Kjaer SK, Konecny GE, Krakstad C, Kupryjanczyk J, Lambrechts D, Lambrechts S, Le ND, Lee N, Lee J, Leminen A, Lim BK, Lissowska J, Lubiński J, Lundvall L, Lurie G, Massuger LF, Matsuo K, McGuire V, McLaughlin JR, Menon U, Modugno F, Moysich KB, Nakanishi T, Narod SA, Ness RB, Nevanlinna H, Nickels S, Noushmehr H, Odunsi K, Olson S, Orlov I, Paul J, Pejovic T, Pelttari LM, Permuth-Wey J, Pike MC, Poole EM, Qu X, Risch HA, Rodriguez-Rodriguez L, Rossing MA, Rudolph A, Runnebaum I, Rzepecka IK, Salvesen HB, Schwaab I, Severi G, Shen H, Shridhar V, Shu XO, Sieh W, Southey MC, Spellman P, Tajima K, Teo SH, Terry KL, Thompson PJ, Timorek A, Tworoger SS, van Altena AM, van den Berg D, Vergote I, Vierkant RA, Vitonis AF, Wang-Gohrke S, Wentzensen N, Whittemore AS, Wik E, Winterhoff B, Woo YL, Wu AH, Yang HP, Zheng W, Ziogas A, Zulkifli F, Goodman MT, Hall P, Easton DF,

- Pearce CL, Berchuck A, Chenevix-Trench G, Iversen E, Monteiro AN, Gayther SA, Schildkraut JM, Sellers TA. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. *Nat Genet.* 2013 Apr;45(4):362-70.
250. Lesnock JL, Darcy KM, Tian C, Deloia JA, Thrall MM, Zahn C, Armstrong DK, **Birrer MJ**, Krivak TC. BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study. *Br J Cancer.* 2013 Apr 2;108(6):1231-7.
 251. Goode EL, DeRycke M, Kalli KR, Oberg AL, Cunningham JM, Maurer MJ, Fridley BL, Armasu SM, Serie DJ, Ramar P, Goergen K, Vierkant RA, Rider DN, Sicotte H, Wang C, Winterhoff B, Phelan CM, Schildkraut JM, Weber RP, Iversen E, Berchuck A, Sutphen R, **Birrer MJ**, Hampras S, Preus L, Gayther SA, Ramus SJ, Wentzensen N, Yang HP, Garcia-Closas M, Song H, Tyrer J, Pharoah PP, Konecny G, Sellers TA, Ness RB, Sucheston LE, Odunsi K, Hartmann LC, Moysich KB, Knutson KL. Inherited variants in regulatory T cell genes and outcome of ovarian cancer. *PLoS One.* 2013;8(1):e53903.
 252. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER, Levine DA. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013 May 2;497(7447):67-73.
 253. Bradford LS, Rauh-Hain JA, Schorge J, **Birrer MJ**, Dizon DS. Advances in the Management of Recurrent Endometrial Cancer. *Am J Clin Oncol.* 2013 Jun 11; PubMed PMID:23764681
 254. Holderness Parker N, Donniger H, **Birrer MJ**, Leaner VD. p21-activated kinase 3 (PAK3) is an AP-1 regulated gene contributing to actin organisation and migration of transformed fibroblasts. *PLoS One.* 2013 Jun 20;8(6):e66892. doi:10.1371/journal.pone.0066892. Print 2013. PubMed PMID: 23818969
 255. Yeung TL, Leung CS, Wong KK, Samimi G, Thompson MS, Liu J, Zaid TM, Ghosh S, **Birrer MJ**, Mok SC. TGF- β modulates ovarian cancer invasion by upregulating CAF-derived versican in the tumor micro-environment. *Cancer Res.* 2013 Aug 15;73(16):5016-28. doi: 10.1158/0008-5472.CAN-13-0023. Epub 2013 Jul 3. PubMed PMID: 23824740; PubMed Central PMCID: PMC3745588.
 256. Liu JF, Tolaney SM, **Birrer M**, Fleming GF, Buss MK, Dahlberg SE, Lee H, Whalen C, Tyburski K, Winer E, Ivy P, Matulonis UA. A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. *Eur J Cancer.* 2013 Sep;49(14):2972-8. doi:10.1016/j.ejca.2013.05.020. Epub 2013 Jun 27. PubMed PMID: 23810467.
 257. He L, Guo L, Vathipadiekal V, Sergeant PA, Growdon WB, Engler DA, Rueda BR, **Birrer MJ**, Orsulic S, Mohapatra G. Identification of LMX1B as a novel oncogene in human ovarian cancer. *Oncogene.* 2013 Sep 23. doi: 10.1038/onc.2013.375. PubMed PMID: 24056967.

258. Rauh-Hain JA, Guseh SH, Esselen KM, Growdon WB, Schorge JO, Horowitz NS, Krasner CN, del Carmen MG, **Birrer MJ**, Dizon DS. Patterns of recurrence in patients treated with bevacizumab in the primary treatment of advanced epithelial ovarian cancer. *Int J Gynecol Cancer*. 2013 Sep;23(7):1219-25.
259. Penson RT, Dizon DS, **Birrer MJ**. Clear cell cancer of the ovary. *Curr Opin Oncol*. 2013 Sep;25(5):553-7. doi: 10.1097/CCO.0b013e328363e0c7. PubMed PMID: 23942300.
260. Levanon K, Sapoznik S, Bahar-Shany K, Brand H, Shapira-Frommer R, Korach J, Hirsch MS, Roh MH, Miron A, Liu JF, Vena N, Ligon AH, Fotheringham S, Bailey D, Flavin RJ, **Birrer MJ**, Drapkin RI. FOXO3a loss is a frequent early event in high-grade pelvic serous carcinogenesis. *Oncogene*. 2013 Sep 30. doi:10.1038/onc.2013.394. PubMed PMID: 24077281.
261. Wei W, Mok SC, Oliva E, Kim SH, Mohapatra G, **Birrer MJ**. FGF18 as a prognostic and therapeutic biomarker in ovarian cancer. *J Clin Invest*. 2013 Oct 1;123(10):4435-48. doi: 10.1172/JCI70625. Epub 2013 Sep 9. PubMed PMID: 24018557; PubMed Central PMCID: PMC3784549.
262. Creutzberg CL, Kitchener HC, **Birrer MJ**, Landoni F, Lu KH, Powell M, Aghajanian C, Edmondson R, Goodfellow PJ, Quinn M, Salvesen HB, Thomas G. GCIG Endometrial Cancer Clinical Trials Planning Meeting. Gynecologic Cancer InterGroup (GCIG) endometrial cancer clinical trials planning meeting: taking endometrial cancer trials into the translational era. *Int J Gynecol Cancer*. 2013 Oct;23(8):1528-34. doi: 10.1097/IGC.0b013e3182a26edb. PubMed PMID: 24257568.
263. Dizon DS, Ambrosio AJ, Feltmate C, Wright AA, Campos SM, Viswanathan A. Cervical Cancer Special Interest Group of Dana-Farber/Harvard Comprehensive Cancer Center Gynecologic Cancer Management Team. Pushing the bar in treatment of cervical cancer: what can comprehensive cancer centers do on their own? *Gynecol Oncol*. 2013 Nov;131(2):464-6. doi: 10.1016/j.ygyno.2013.08.002. Epub 2013 Aug 9. PubMed PMID: 23938373.
264. Tanwar PS, Mohapatra G, Chiang S, Engler DA, Zhang L, Kaneko-Tarui T, Ohguchi Y, **Birrer MJ**, Teixeira JM. Loss of LKB1 and PTEN tumor suppressor genes in the ovarian surface epithelium induces papillary serous ovarian cancer. *Carcinogenesis*. 2013 Dec 2. PubMed PMID: 24170201.
265. Peterson VM, Castro CM, Chung J, Miller NC, Ullal AV, Castano MD, Penson RT, Lee H, **Birrer MJ**, Weissleder R. Ascites analysis by a microfluidic chip allows tumor-cell profiling. *Proc Natl Acad Sci U S A*. 2013 Dec 17;110(51):E4978-86. doi:10.1073/pnas.1315370110. Epub 2013 Dec 2. PubMed PMID: 24297935.
266. Wei W, Dizon D, Vathipadiekal V, **Birrer MJ**. Ovarian cancer: genomic analysis. *Ann Oncol*. 2013 Dec; 24 Suppl 10:x7-x15. doi: 10.1093/annonc/mdt462. PubMed PMID: 24265410; PubMed Central PMCID: PMC3836569.
267. Jeong W, Kim SB, Sohn BH, Park YY, Park ES, Kim SC, Kim SS, Johnson RL, **Birrer M**, Bowtell DS, Mills GB, Sood A, Lee JS. Activation of YAP1 Is Associated with Poor Prognosis and

- Response to Taxanes in Ovarian Cancer. *Anticancer Res.* 2014 Feb;34(2):811-7. PubMed PMID: 24511017
268. Bookman MA, Gilks CB, Kohn EC, Kaplan KO, Huntsman D, Aghajanian C, **Birrer MJ**, Ledermann JA, Oza AM, Sweneron KD. Better therapeutic trials in ovarian cancer. *J Natl Cancer Inst.* 2014 April 1;106(4).
 269. Riester M, Wei W, Waldron L, Culhane AC, Trippa L, Oliva E, Kim S, Michor F, Hutterenhower C, Parmigiani G, **Birrer MJ**. Risk prediction for late-stage ovarian cancer by meta-analysis of 1525 patient samples. *J Natl Cancer Instit.* 2014 April 3;106(5): dju 048. April 3 Pubmed PMID: 24700803.
 270. Waldron L, Haibe-Kains B, Culhane AC, Riester M, Ding J, Wang XV, Ahmadifar M, Tyekucheva S, Bernau C, Risch T, Ganzfried BF, Hutterhower C, **Birrer MJ**, Parmigiani G. Comparative meta-analysis of prognostic gene signatures for late-stage ovarian cancer. *J Natl Cancer Instit.* 2014 April 3;106(5): dju 049.
 271. **Birrer MJ**. Ovarian cancer: targeting the untargetable. *Am Soc Clin Oncol Educ Book.* 2014;34:13-5.
 272. Dizon DS, **Birrer MJ**. Advances in the diagnosis and treatment of uterine sarcomas. *Disc Med.* 2014 Jun;17(96):339-45.
 273. Leung CS, Yeung TL, Yip KP, Pradeep S, Balasubramanian L, Liu J, Wong KK, Mangala LS, Armaiz-Pena GN, Lopez-Berestein G, Sood AK, **Birrer MJ**, Mok SC. Calcium dependent FAK/CREB/TNNC1 signaling mediates the effect of stromal MFAP% on ovarian cancer metastatic potential. *Nat Commun* 2014, Oct 3;5:5092. PMCID: PMC4185407.
 274. Matulonis U, Vergote I, Backes F, Martin LP, McMeekin S, **Birrer M**, Campana F, Xu Y, Egile C, Ghamande S. Phase II study of the P13K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. *Gynecol Oncol.* 2014 Dec 17. pii: S0090-8258(14)01574-1. doi: 10.1016/j.ygyno.2014.12.019.
 275. Ghosh D, Bagley AF, NaYJ, **Birrer MJ**, Bhatia SN, Beleher AM. Deep, noninvasive imaging and surgical guidance of submillimeter tumors using targeted M13-stabilized single-walled carbon nanotubes. *Proc Natl Acad Sci USA.* 2014 Sep 23;111(38):13948-53. doi:10.1073/pnas.1400821111. Epub 2014 Sept. 1.
 276. Liu JF, Barry WT, **Birrer M**, Lee JM, Buckanovich RJ, Fleming GF, Rimel B, Buss MK, Nattam S, Hurteau J, Luo W, Quy P, Whalen C, Obermayer L, Lee H, Winer EP, Kohn EC, Ivy SP, Matulonis UA. *Lancet Oncol.* 2014 Oct. 15(11):1207-14. doi: 10.1016/S1470-2045(14)70391-2. Epub 2014 Sept 10.
 277. Waldron L, Reister M, **Birrer MJ**. Molecular subtypes of high-grade serous ovarian cancer: the holy grail? *J Natl Cancer Inst.* 2014 Sept. 30;106(10). Pii: dju297. doi: 210.1093/jcni/dju297. Print 2014 Oct.

278. Pham E, **Birrer MJ**, Eliasof S, Garmey E, Lazarus D, Lee CR, Man S, Matulonis UA, Peters CG, Xu P, Krasner C, Kerbel RS. Translational impact of nanoparticle-drug conjugate CRLX101 with or without bevacizumab in advanced ovarian cancer. *Clin Cancer Res*. 2015 Feb 15; 21(4):808-18.
279. Matulonis U, Vergote I, Backes F, Martin LP, McMeekin S, **Birrer M**, Campana F, Xu Y, Egile C, Ghamande S. Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. *Gynecol Oncol*. 2015 Feb;136(2):246-53. doi: 10.1016/j.ygyno.2014.12.019. Epub 2014 Dec 17.
280. Castro CM, Im H, Le C, Lee H, Weissleder R, **Birrer MJ**. Exploring alternative ovarian cancer biomarkers using innovative nanotechnology strategies. *Cancer Metastasis Rev*. 2015 Mar;34(1):75-82. doi: 10.1007/s10555-014-9546-9.
281. Tyekucheva S, Martin NE, Stack EC, Wei W, Vathipadiekal V, Waldron L, Fiorentino M, Lis RT, Stampfer MJ, Loda M, Parmigiani G, Mucci LA, **Birrer M**. Comparing Platforms for Messenger RNA Expression Profiling of Archival Formalin-Fixed, Paraffin-Embedded Tissues. *J Mol Diagn*. 2015 Jul;17(4):374-81. doi: 10.1016/j.jmoldx.2015.02.002. Epub 2015 Apr 30.
282. Vathipadiekal V, Wang V, Wei W, Waldron L, Drapkin R, Gillette M, Skates S, **Birrer M**. Creation of a Human Secretome: A Novel Composite Library of Human Secreted Proteins: Validation Using Ovarian Cancer Gene Expression Data and a Virtual Secretome Array. *Clin Cancer Res*. 2015 May 5
283. Elagib KE, Xiao M, Hussaini IM, Delehanty LL, Palmer LA, Racke FK, **Birrer MJ**, Ganapathy-Kanniappan S, McDevitt MA, Goldfarb AN. Erratum for Elagib et al., Jun blockade of erythropoiesis: role for repression of GATA-1 by HERP2. *Mol Cell Biol*. 2015 Jun;35(12):2215. doi: 10.1128/MCB.00374-15.
284. Wei W, **Birrer MJ**. Spleen Tyrosine Kinase Confers Paclitaxel Resistance in Ovarian Cancer. *Cancer Cell*. 2015 Jul 13;28(1):7-9. doi: 10.1016/j.ccell.2015.06.008.
285. Pépin D, Sosulski A, Zhang L, Wang D, Vathipadiekal V, Hendren K, Coletti CM, Yu A, Castro, CM, **Birrer MJ**, Gao G, Donahoe PK. AAV9 delivering a modified human Mullerian inhibiting substance as a gene therapy in patient-derived xenografts of ovarian cancer. *Proc Natl Acad Sci U S A*. 2015 Aug 11;112(32):E4418-27. doi: 10.1073/pnas.1510604112. Epub 2015 Jul 27.
286. Richards EJ, Permeth-Wey J, Li Y, Chen YA, Coppola D, Reid BM, Lin HY, Teer JK, Berchuck A, **Birrer MJ**, Lawrenson K, Monteiro AN, Schildkraut JM, Goode EL, Gayther SA, Sellers TA, Cheng JQ. A functional variant in HOXA11-AS, a novel long non-coding RNA, inhibits the oncogenic phenotype of epithelial ovarian cancer. *Oncotarget*. 2015 Sep 22.
287. Bowtell DD, Böhm S, Ahmed AA, Aspuria PJ, Bast RC Jr, Beral V, Berek JS, **Birrer MJ**, Blagden S, Bookman MA, Brenton JD, Chiappinelli KB, Martins FC, Coukos G, Drapkin R, Edmondson R, Fotopoulou C, Gabra H, Galon J, Gourley C, Heong V, Huntsman DG, Iwanicki M, Karlan BY, Kaye A, Lengyel E, Levine DA, Lu KH, McNeish IA, Menon U, Narod SA, Nelson BH, Nephew

- KP, Pharoah P, Powell DJ Jr, Ramos P, Romero IL, Scott CL, Sood AK, Stronach EA, Balkwill FR. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. *Nat Rev Cancer*. 2015 Oct 23;15(11):668-79. doi: 10.1038/nrc4019.
288. Sarantopoulos J, Mita MM, **Birrer MJ**, Cranmer LD, Campos LT, Zhang X, Bristow P, Kaito H, Strout V, Camacho LH. Phase 1 Study of monotherapy with KHK2866, an anti-heparin-binding epidermal growth factor-like growth factor monoclonal antibody, in patients with advanced cancer. *Target Oncol*. 2015 Oct 27.
 289. Ye H, Tanenbaum LM, Na YJ, Mantzavinou A, Fulci G, Del Carmen MG, **Birrer MJ**, Cima MJ. Sustained, low-dose intraperitoneal cisplatin improves treatment outcome in ovarian cancer mouse models. *J Control Release*. 2015 Dec 28;220(Pt A):358-67. doi: 10.1016/j.jconrel.2015.11.001. Epub 2015 Nov 5.
 290. Moran-Jones K, Gloss BS, Murali R, Chang DK, Colvin EK, Jones MD, Yuen S, Howell VM, Brown LM, Wong CW, Spong SM, Scarlett CJ, Hacker NF, Ghosh S, Mok SC, **Birrer MJ**, Samimi G. Connective tissue growth factor as a novel therapeutic target in high grade serous ovarian cancer. *Oncotarget*. 2015 Nov 11. doi: 10.18632/oncotarget.6082.
 291. Bolton KL, Tyrer J, Song H, Ramus SJ, Notaridou M, Jones C, Sher T, Gentry-Maharaj A, Wozniak E, Tsai YY, Weidhaas J, Paik D, Van Den Berg DJ, Stram DO, Pearce CL, Wu AH, Brewster W, Anton-Culver H, Ziogas A, Narod SA, Levine DA, Kaye SB, Brown R, Paul J, Flanagan J, Sieh W, McGuire V, Whittemore AS, Campbell I, Gore ME, Lissowska J, Yang HP, Medrek K, Gronwald J, Lubinski J, Jakubowska A, Le ND, Cook LS, Kelemen LE, Brooks-Wilson A, Massuger LF, Kiemeny LA, Aben KK, van Altena AM, Houlston R, Tomlinson I, Palmieri RT, Moorman PG, Schildkraut J, Iversen ES, Phelan C, Vierkant RA, Cunningham JM, Goode EL, Fridley BL, Kruger-Kjaer S, Blaeker J, Hogdall E, Hogdall C, Gross J, Karlan BY, Ness RB, Edwards RP, Odunsi K, Moyisch KB, Baker JA, Modugno F, Heikkinen T, Butzow R, Nevanlinna H, Leminen A, Bogdanova N, Antonenkova N, Doerk T, Hillemanns P, Dürst M, Runnebaum I, Thompson PJ, Carney ME, Goodman MT, Lurie G, Wang-Gohrke S, Hein R, Chang-Claude J, Rossing MA, Cushing-Haugen KL, Doherty J, Chen C, Rafnar T, Besenbacher S, Sulem P, Stefansson K, **Birrer MJ**, Terry KL, Hernandez D, Cramer DW, Vergote I, Amant F, Lambrechts D, Despiere E, Fasching PA, Beckmann MW, Thiel FC, Ekici AB, Chen X; Australian Ovarian Cancer Study Group, Johnatty SE, Webb PM, Beesley J, Chanock S, Garcia-Closas M, Sellers T, Easton DF, Berchuck A, Chenevix-Trench G, Pharoah PD, Gayther SA. Corrigendum: Common variants at 19p13 are associated with susceptibility to ovarian cancer. *Nat Genet*. 2015 Dec 29;48(1):101. doi: 10.1038/ng0116-101b.
 292. Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S, Bernards SS, Casadei S, Yi Q, Burger RA, Chan JK, Davidson SA, Mannel RS, DiSilvestro PA, Lankes HA, Ramirez NC, King MC, Swisher EM, **Birrer MJ**. Inherited mutations in women with ovarian carcinoma. *JAMA Oncol*. 2015 Dec 30:1-9. doi: 10.1001/jamaoncol.2015.5495.
 293. van der Watt PJ, Chi A, Stelma T, Stowell C, Strydom E, Carden S, Angus L, Hadley K, Lang D, Wei W, **Birrer MJ**, Trent JO, Leaner VD. Targeting the nuclear import receptor, Kpnβ1 as an anti-cancer therapeutic. *Mol Cancer Ther*. 2016 Feb 1. pii: molcanther.0052.2015.

294. Dizon DS, **Birrer MJ**. Making a difference: Distinguishing two primaries from metastasis in synchronous tumors of the ovary and uterus. *J Natl Cancer Inst*. 2016 Feb 1;108(6). pii: djv442. doi: 10.1093/jnci/djv442. Print 2016 Jun.
295. Chan JK, Brady MF, Penson RT, Huang H, **Birrer MJ**, Walker JL, DiSilvestro PA, Rubin SC, Martin LP, Davidson SA, Huh WK, O'Malley DM, Boente MP, Michael H, Monk BJ. Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. *N Engl J Med*. 2016 Feb 25;374(8):738-48. doi: 10.1056/NEJMoa1505067.
296. Swisher EM, Harrell MI, Norquist BM, Walsh T, Brady M, Lee M, Hershberg R, Kalli KR, Lankes H, Konnick EQ, Pritchard CC, Monk BJ, Chan JK, Burger R, Kaufmann SH, **Birrer MJ**. Somatic mosaic mutations in PPM1D and TP53 in the blood of women with ovarian carcinoma. *JAMA Oncol*. 2016 Feb 4. doi: 10.1001/jamaoncol.2015.6053.
297. Penson RT, Sales E, Sullivan L, Borger DR, Krasner CN, Goodman AK, Del Carmen MG, Growdon WB, Schorge JO, Boruta DM, Castro CM, Dizon DS, **Birrer MJ**. A SNaPshot of potentially personalized care: Molecular diagnostics in gynecologic cancer. *Gynecol Oncol*. 2016 Apr;141(1):108-12. doi: 10.1016/j.ygyno.2016.02.032.
298. Myers AP, Filiaci VL, Zhang Y, Pearl M, Behbakht K, Makker V, Hanjani P, Zweizig S, Burke JJ 2nd, Downey G, Leslie KK, Van Hummelen P, **Birrer MJ**, Fleming GF. Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer (EC): An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol*. 2016 Apr;141(1):43-8. doi: 10.1016/j.ygyno.2016.02.025.
299. Krzystyniak J, Ceppi L, Dizon DS, **Birrer MJ**. Epithelial ovarian cancer: the molecular genetics of epithelial ovarian cancer. *Ann Oncol*. 2016 Apr;27 Suppl 1:i4-i10. doi: 10.1093/annonc/mdw083.
300. Sosulski A, Horn H, Zhang L, Coletti C, Vathipadiekal V, Castro CM, **Birrer MJ**, Nagano O, Saya H, Lage K, Donahoe PK, Pépin D. CD44 Splice Variant v8-10 as a Marker of Serous Ovarian Cancer Prognosis. *PLoS One*. 2016 Jun 2;11(6):e0156595. doi: 10.1371/journal.pone.0156595. eCollection 2016.
301. Lax T, Dizon DS, **Birrer M**, Long A, Del Carmen M, Goodman A, Krasner C, Penson RT, Growdon W, Camargo CA Jr, Banerji A. Extended carboplatin infusion does not reduce frequency of hypersensitivity reaction at initiation of retreatment in patients with recurrent platinum-sensitive ovarian cancer. *J Allergy Clin Immunol Pract*. 2017 Jan - Feb;5(1):177-178. doi: 10.1016/j.jaip.2016.07.010. No abstract available.
302. Waldron L, Riester M, Ramos M, Parmigiani G, **Birrer M**. The Doppelgänger effect: Hidden duplicates in databases of transcriptome profiles. *J Natl Cancer Inst*. 2016 Jul 5;108(11). pii: djw146. doi: 10.1093/jnci/djw146.

303. Wilbur MB, **Birrer MJ**, Spriggs DR. CLINICAL DECISIONS. Chemotherapy-Induced Nausea and Vomiting. *N Engl J Med*. 2016 Jul 14;375(2):177-9. doi: 10.1056/NEJMcldel607577. No abstract available.
304. Rauh-Hain JA, **Birrer M**, Del Carmen MG. "Carcinosarcoma of the ovary, fallopian tube, and peritoneum: Prognostic factors and treatment modalities". *Gynecol Oncol*. 2016 Aug;142(2):248-54. doi: 10.1016/j.ygyno.2016.06.003.
305. Del Carmen MG, Supko JG, Horick NK, Rauh-Hain JA, Clark RM, Campos SM, Krasner CN, Atkinson T, **Birrer MJ**. Phase 1 and 2 study of carboplatin and pralatrexate in patients with recurrent, platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. *Cancer*. 2016 Nov 15;122(21):3297-3306. doi: 10.1002/encr.30196.
306. Liu JF, Moore KN, **Birrer MJ**, Berlin S, Matulonis UA, Infante JR, Wolpin B, Poon KA, Firestein R, Xu J, Kahn R, Wang Y, Wood K, Darbonne WC, Lackner MR, Kelley SK, Lu X, Choi YJ, Maslyar D, Humke EW, Burris HA. Phase I study of safety and pharmacokinetics of the anti-MUC16 antibody-drug conjugate DMUC5754A in patients with platinum-resistant ovarian cancer or unresectable pancreatic cancer. *Ann Oncol*. 2016 Nov;27(11):2124-2130.
307. Matulonis UA, Wulf GM, Barry WT, **Birrer M**, Westin SN, Farooq S, Bell-McGuinn KM, Obermayer E, Whalen C, Spagnoletti T, Luo W, Liu H, Hok RC, Aghajanian C, Solit DB, Mills GB, Taylor BS, Won H, Berger MF, Palakurthi S, Liu J, Cantley LC, Winer E. Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high grade serous ovarian and breast cancer. *Ann Oncol*. 2016 Dec 19. pii: mdw672. doi: 10.1093/annonc/mdw672.
308. Moore KN, Martin LP, O'Malley DM, Matulonis UA, Konner JA, Perez RP, Bauer TM, Ruiz-Soto R, **Birrer MJ**. Safety and activity of mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: A phase I expansion study. *J Clin Oncol*. 2016 Dec 28;JCO2016699538.
309. McCourt CK, Deng W, Dizon DS, Lankes HA, **Birrer MJ**, Lomme MM, Powell MA, Kendrick JE, Saltzman JN, Warshal D, Tenney ME, Kushner DM, Aghajanian C. A phase II evaluation of ixabepilone in the treatment of recurrent/persistent carcinosarcoma of the uterus, an NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol*. 2017 Jan;144(1):101-106. doi: 10.1016/j.ygyno.2016.10.026.
310. Cancer Genome Atlas Research Network. Integrated genomic and molecular characterization of cervical cancer. *Nature*. 2017 Jan 23. doi: 10.1038/nature21386.
311. Xiao H, Qi R, Li T, Awuah SG, Zheng Y, Wei W, Kang X, Song H, Wang Y, Yu Y, Bird MA, Jing X, Yaffe MB, **Birrer MJ**, Ghoroghchian PP. Maximizing Synergistic Activity When Combining RNAi and Platinum-based Anticancer Agents. *J Am Chem Soc*. 2017 Feb 6. doi: 10.1021/jacs.6b12108.

312. Gockley A, Melamed A, Bregar AJ, Clemmer JT, **Birrer M**, Schorge JO, Del Carmen MG, Rauh-Hain JA. Outcomes of women with high-grade and low-grade advanced-stage serous epithelial ovarian cancer. *Obstet Gynecol.* 2017 Mar;129(3):439-447. doi:
313. Yazinski SA, Comaills V, Buisson R, Genois MM, Nguyen HD, Ho CK, Todorova Kwan T, Morris R, Lauffer S, Nussenzweig A, Ramaswamy S, Benes CH, Haber DA, Maheswaran S, **Birrer MJ**, Zou L. ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells. *Genes Dev.* 2017 Feb 1;31(3):318-332. doi: 10.1101/gad.290957.116. Epub 2017 Feb 27.
314. Phelan CM, Kuchenbaecker KB, Tyrer JP, Kar SP, Lawrenson K, Winham SJ, Dennis J, Pirie A, Riggan MJ, Chornokur G, Earp MA, Lyra PC Jr, Lee JM, Coetzee S, Beesley J, McGuffog L, Soucy P, Dicks E, Lee A, Barrowdale D, Lecarpentier J, Leslie G, Aalfs CM, Aben KK, Adams M, Adlard J, Andrulis IL, Anton-Culver H, Antonenkova N; AOCS study group., Aravantinos G, Arnold N, Arun BK, Arver B, Azzollini J, Balmaña J, Banerjee SN, Barjhoux L, Barkardottir RB, Bean Y, Beckmann MW, Beeghly-Fadiel A, Benitez J, Bermisheva M, Bernardini MQ, **Birrer MJ**, Bjorge L, Black A, Blankstein K, Blok MJ, Bodelon C, Bogdanova N, Bojesen A, Bonanni B, Borg Å, Bradbury AR, Brenton JD, Brewer C, Brinton L, Broberg P, Brooks-Wilson A, Bruinsma F, Brunet J, Buecher B, Butzow R, Buys SS, Caldes T, Caligo MA, Campbell I, Cannioto R, Carney ME, Cescon T, Chan SB, Chang-Claude J, Chanock S, Chen XQ, Chiew YE, Chiquette J, Chung WK, Claes KB, Conner T, Cook LS, Cook J, Cramer DW, Cunningham JM, D'Aloisio AA, Daly MB, Damiola F, Damirova SD, Dansonka-Mieszkowska A, Dao F, Davidson R, DeFazio A, Delnatte C, Doheny KF, Diez O, Ding YC, Doherty JA, Domchek SM, Dorfling CM, Dörk T, Dossus L, Duran M, Dürst M, Dworniczak B, Eccles D, Edwards T, Eeles R, Eilber U, Ejlersen B, Ekici AB, Ellis S, Elvira M; EMBRACE Study., Eng KH, Engel C, Evans DG, Fasching PA, Ferguson S, Ferrer SF, Flanagan JM, Fogarty ZC, Fortner RT, Fostira F, Foulkes WD, Fountzilas G, Fridley BL, Friebel TM, Friedman E, Frost D, Ganz PA, Garber J, García MJ, Garcia-Barberan V, Gehrig A; GEMO Study Collaborators., Gentry-Maharaj A, Gerdes AM, Giles GG, Glasspool R, Glendon G, Godwin AK, Goldgar DE, Goranova T, Gore M, Greene MH, Gronwald J, Gruber S, Hahnen E, Haiman CA, Håkansson N, Hamann U, Hansen TV, Harrington PA, Harris HR, Hauke J; HEBON Study., Hein A, Henderson A, Hildebrandt MA, Hillemanns P, Hodgson S, Høgdall CK, Høgdall E, Hogervorst FB, Holland H, Hoening MJ, Hosking K, Huang RY, Hulick PJ, Hung J, Hunter DJ, Huntsman DG, Huzarski T, Imyanitov EN, Isaacs C, Iversen ES, Izatt L, Izquierdo A, Jakubowska A, James P, Janavicius R, Jernetz M, Jensen A, Jensen UB, John EM, Johnatty S, Jones ME, Kannisto P, Karlan BY, Karnezis A, Kast K; KConFab Investigators., Kennedy CJ, Khusnutdinova E, Kiemeny LA, Kiiski JI, Kim SW, Kjaer SK, Köbel M, Kopperud RK, Kruse TA, Kupryjanczyk J, Kwong A, Laitman Y, Lambrechts D, Larrañaga N, Larson MC, Lazaro C, Le ND, Le Marchand L, Lee JW, Lele SB, Leminen A, Leroux D, Lester J, Lesueur F, Levine DA, Liang D, Liebrich C, Lilyquist J, Lipworth L, Lissowska J, Lu KH, Lubinński J, Luccarini C, Lundvall L, Mai PL, Mendoza-Fandiño G, Manoukian S, Massuger LF, May T, Mazoyer S, McAlpine JN, McGuire V, McLaughlin JR, McNeish I, Meijers-Heijboer H, Meindl A, Menon U, Mensenkamp AR, Merritt MA, Milne RL, Mitchell G, Modugno F, Moes-Sosnowska J, Moffitt M, Montagna M, Moysich KB, Mulligan AM, Musinsky J, Nathanson KL, Nedergaard L, Ness RB, Neuhausen SL, Nevanlinna H, Niederacher D, Nussbaum RL, Odunsi K, Olah E, Olopade OI, Olsson H, Olswold C, O'Malley DM, Ong KR, Onland-Moret NC; OPAL study group., Orr N, Orsulic S, Osorio A, Palli D, Papi L, Park-Simon TW, Paul J, Pearce CL, Pedersen IS, Peeters PH, Peissel B, Peixoto A, Pejovic T, Pelttari LM,

- Permuth JB, Peterlongo P, Pezzani L, Pfeiler G, Phillips KA, Piedmonte M, Pike MC, Piskorz AM, Poblete SR, Pocza T, Poole EM, Poppe B, Porteous ME, Prieur F, Prokofyeva D, Pugh E, Pujana MA, Pujol P, Radice P, Rantala J, Rappaport-Fuerhauser C, Rennert G, Rhiem K, Rice P, Richardson A, Robson M, Rodriguez GC, Rodriguez-Antona C, Romm J, Rookus MA, Rossing MA, Rothstein JH, Rudolph A, Runnebaum IB, Salvesen HB, Sandler DP, Schoemaker MJ, Senter L, Setiawan VW, Severi G, Sharma P, Shelford T, Siddiqui N, Side LE, Sieh W, Singer CF, Sobol H, Song H, Southey MC, Spurdle AB, Stadler Z, Steinemann D, Stoppa-Lyonnet D, Sucheston-Campbell LE, Sukiennicki G, Sutphen R, Sutter C, Swerdlow AJ, Szabo CI, Szafron L, Tan YY, Taylor JA, Tea MK, Teixeira MR, Teo SH, Terry KL, Thompson PJ, Thomsen LC, Thull DL, Tihomirova L, Tinker AV, Tischkowitz M, Tognazzo S, Toland AE, Tone A, Trabert B, Travis RC, Trichopoulou A, Tung N, Tworoger SS, van Altena AM, Van Den Berg D, van der Hout AH, van der Luijt RB, Van Heetvelde M, Van Nieuwenhuysen E, van Rensburg EJ, Vanderstichele A, Varon-Mateeva R, Vega A, Edwards DV, Vergote I, Vierkant RA, Vijai J, Vratimos A, Walker L, Walsh C, Wand D, Wang-Gohrke S, Wappenschmidt B, Webb PM, Weinberg CR, Weitzel JN, Wentzensen N, Whittemore AS, Wijnen JT, Wilkens LR, Wolk A, Woo M, Wu X, Wu AH, Yang H, Yannoukakos D, Ziogas A, Zorn KK, Narod SA, Easton DF, Amos CI, Schildkraut JM, Ramus SJ, Ottini L, Goodman MT, Park SK, Kelemen LE, Risch HA, Thomassen M, Offit K, Simard J, Schmutzler RK, Hazelett D, Monteiro AN, Couch FJ, Berchuck A, Chenevix-Trench G, Goode EL, Sellers TA, Gayther SA, Antoniou AC, Pharoah PD. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. *Nat Genet.* 2017 Mar 27. doi: 10.1038/ng.3826.
315. Moore KN, Borghaei H, O'Malley DM, Jeong W, Seward SM, Bauer TM, Perez RP, Matulonis UA, Running KL, Zhang X, Ponte JF, Ruiz-Soto R, **Birrer MJ**. Phase 1 dose-excalation study of mirvetuximab soravtansine (IMGN853), a folate receptor α -targeting antibody-drug conjugate, in patients with solid tumors. *Cancer* 2017 Apr 25. doi: 10.1002/cncr.30736.
316. Tao Z, Dang X, Huang X, Muzumdar MD, Xu ES, Neelkanth NM, Song H, Qi R, Yu Y, Li T, Wei W, Wyckoff J, **Birrer MJ**, Belcher AM, Ghoroghchian PP. Early tumor detection afforded by *in vivo* imaging of near infrared II fluorescence. *Biomaterials* 134 July 2017, 202-215 doi: 10.1016/j.biomaterials. 2017.04.046.
317. Reyes HD, Miecznikowski J, Gonzalez-Bosquet J, Devor EJ, Zhang Y, Thiel KW, Samuelson MI, McDonald M, stephan JM, Hanjani P, Guntupalli S, Tewari KS, Backes F, Ramirez N, Fleming GF, Filiaci V, **Birrer MJ**, Leslie KK. High stathmin expression is a marker for poor clinical outcome in endometrial cancer: An NRG oncology group/gynecologic oncology group study. *Gynecol Oncol.* 2017, May 19 pii: S0090-8258(17)30870-3. Doi: 10.1016/j.ygyno.2017.05.017.
318. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leita MM, Michael HE, DiSaia PJ, Copeland LJ, Creasman WT, Stehman FB, Brady MF, Burger RA, Thigpen JT, **Birrer MJ**, Waggoner SE, Moore DH, Look KY, Koh WJ, Monk BJ. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet.* 2017 Jul 27. pii: S0140-6736(17)31607-0. doi: 10.1016/S0140-6736(17)31607-0.
319. Martin LP, Konner JA, Moore KN, Seward SM, Matulonis UA, Perez RP, Su Y, Berkenblit A, Ruiz-Soto R, **Birrer MJ**. Characterization of folate receptor alpha (FR α) expression in archival

tumor and biopsy samples from relapsed epithelial ovarian cancer patients: A phase I expansion study of the FR α -targeting antibody-drug conjugate mirvetuximab soravtansine. *Gynecol Oncol.* 2017 Aug 24. pii: S0090-8258(17)31253-2. doi: 10.1016/j.ygyno.2017.08.015.

320. Moore KN, Trichtler D, Kaufman KM, Lankes H, Quinn MCJ; Ovarian Cancer Association Consortium, Van Le L, Berchuck A, Backes FJ, Tewari KS, Lee RB, Kesterson JP, Wenham RM, Armstrong DK, Krivak TC, Bookman MA, **Birrer MJ**. Genome-wide association study evaluating single-nucleotide polymorphisms and outcomes in patients with advanced stage serous ovarian or primary peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 2017 Sep 18. pii: S0090-8258(17)31261-1. doi: 10.1016/j.ygyno.2017.08.024.
321. Devor EJ, Miecznikowski J, Schickling BM, Gonzalez-Bosquet J, Lankes HA, Thaker P, Argenta PA, Pearl ML, Zweizig SL, Mannel RS, Brown A, Ramirez NC, Ioffe OB, Park KJ, Creasman WT, **Birrer MJ**, Mutch D, Leslie KK. Dysregulation of miR-181c expression influences recurrence of endometrial endometrioid adenocarcinoma by modulating NOTCH2 expression: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 2017 Sep 29. pii: S0090-8258(17)31349-5. doi: 10.1016/j.ygyno.2017.09.025.
322. Bais C, Mueller B, Brady MF, Mannel RS, Burger RA, Wei W, Marien KM, Kockx MM, Husain A, **Birrer MJ**; Tumor Microvessel Density as a Potential Predictive Marker for Bevacizumab Benefit: GOG-0218 Biomarker Analyses. NRG Oncology/Gynecologic Oncology Group. *J Natl Cancer Inst.* 2017 Nov 1;109(11). doi: 10.1093/jnci/djx066.
323. Tsang TY, Wei W, Itamochi H, Tambouret R, **Birrer MJ**. Integrated genomic analysis of clear cell ovarian cancers identified PRKCI as a potential therapeutic target. *Oncotarget.* 2017 Aug 4;8(57):96482-96495. doi: 10.18632/oncotarget.19946. eCollection 2017 Nov 14. PMID: 29228547
324. Moore KN, Martin LP, O'Malley DM, Matulonis UA, Konner JA, Vergote I, Ponte JF, **Birrer MJ**. A review of mirvetuximab soravtansine in the treatment of platinum-resistant ovarian cancer. *Future Oncol.* 2018 Jan;14(2):123-136. doi: 10.2217/fon-2017-0379. Epub 2017 Nov 3.
325. Norquist BM, Brady MF, Harrell MI, Walsh T, Lee MK, Gulsuner S, Bernards SS, Casadei S, Burger RA, Tewari KS, Backes F, Mannel RS, Glaser G, Bailey C, Rubin S, Soper J, Lankes HA, Ramirez NC, King MC, **Birrer MJ**, Swisher EM. Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study. *Clin Cancer Res.* 2017 Nov 30. doi: 10.1158/1078-0432.CCR-17-1327.
326. Noh K, Mangala LS, Han HD, Zhang N, Pradeep S, Wu SY, Ma S, Mora E, Rupaimoole R, Jiang D, Wen Y, Shahzad MMK, Lyons Y, Cho M, Hu W, Nagaraja AS, Haemmerle M, Mak CSL, Chen X, Gharpure KM, Deng H, Xiong W, Kingsley CV, Liu J, Jennings N, **Birrer MJ**, Bouchard RR, Lopez-Berestein G, Coleman RL, An Z, Sood AK. Differential Effects of EGFL6 on Tumor versus Wound Angiogenesis. *Cell Rep.* 2017 Dec 5;21(10):2785-2795. doi: 10.1016/j.celrep.2017.11.020.
327. Tsang TY, Wei W, Itamochi H, Tambouret R, **Birrer MJ**. Integrated genomic analysis of clear cell ovarian cancers identified PRKCI as a potential therapeutic target. *Oncotarget.* 2017 Aug 4;8(57):96482-96495. doi: 10.18632/oncotarget.19946. eCollection 2017 Nov 14.

328. Wei W, Giulia F, Luffer S, Kumar R, Wu B, Tavallai M, Bekele RT, **Birrer MJ**. How can molecular abnormalities influence our clinical approach? *Ann Oncol*. 2017 Nov 1;28(suppl_8):viii16-viii24. doi: 10.1093/annonc/mdx447.
329. Moore KN, Martin LP, O'Malley DM, Matulonis UA, Konner JA, Vergote I, Ponte JF, **Birrer MJ**. A review of mirvetuximab soravtansine in the treatment of platinum-resistant ovarian cancer. *Future Oncol*. 2018 Jan;14(2):123-136. doi: 10.2217/fon-2017-0379. Epub 2017 Nov 3. PMID: 29098867
330. Leung CS, Yeung TL, Yip KP, Wong KK, Ho SY, Mangala LS, Sood AK, Lopez-Berestein G, Sheng J, Wong ST, **Birrer MJ**, Mok SC. Cancer-associated fibroblasts regulate endothelial adhesion protein LPP to promote ovarian cancer chemoresistance. *J Clin Invest*. 2018 Feb 1;128(2):589-606. doi: 10.1172/JCI95200. Epub 2017 Dec 18. PMID: 29251630
331. Qi R, Wang Y, Bruno PM, Xiao H, Yu Y, Li T, Lauffer S, Wei W, Chen Q, Kang X, Song H, Yang X, Huang X, Detappe A, Matulonis U, Pepin D, Hemann MT, **Birrer MJ**, Ghoroghchian PP. Nanoparticle conjugates of a highly potent toxin enhance safety and circumvent platinum resistance in ovarian cancer. *Nat Commun*. 2017 Dec 18;8(1):2166. doi: 10.1038/s41467-017-02390-7. Erratum in: *Nat Commun*. 2018 Feb 7;9(1):628. PMID: 29255160
332. Moore KN, Vergote I, Oaknin A, Colombo N, Banerjee S, Oza A, Pautier P, Malek K, **Birrer MJ**. FORWARD I: a Phase III study of mirvetuximab soravtansine versus chemotherapy in platinum-resistant ovarian cancer. *Future Oncol*. 2018 Feb 9. doi: 10.2217/fon-2017-0646. [Epub ahead of print] PMID: 29424243
333. Hamilton CA, Miller A, Casablanca Y, Horowitz NS, Rungruang B, Krivak TC, Richard SD, Rodriguez N, **Birrer MJ**, Backes FJ, Geller MA, Quinn M, Goodheart MJ, Mutch DG, Kavanagh JJ, Maxwell GL, Bookman MA. Clinicopathologic characteristics associated with long-term survival in advanced epithelial ovarian cancer: an NRG Oncology/Gynecologic Oncology Group ancillary data study. *Gynecol Oncol*. 2018 Feb;148(2):275-280. doi: 10.1016/j.ygyno.2017.11.018.
334. Banerjee S, Oza AM, **Birrer MJ**, Hamilton EP, Hasan J, Leary A, Moore KN, Mackowiak-Matejczyk B, Pikiel J, Ray-Coquard I, Trask P, Lin K, Schuth E, Vaze A, Choi Y, Marsters JC, Maslyar DJ, Lemahieu V, Wang Y, Humke EW, Liu JF. Anti-NAp2b antibody-drug conjugate lifastuzumab vedotin (DNIB0600A) compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer in a randomized, open-label, phase II study. *Ann Oncol*. 2018 Apr 1;29(4):917-923. doi: 10.1093/annonc/mdy023. PMID: 29401246
335. Norquist BM, Brady MF, Harrell MI, Walsh T, Lee MK, Gulsuner S, Bernards SS, Casadei S, Burger RA, Tewari KS, Backes F, Mannel RS, Glaser G, Bailey C, Rubin S, Soper J, Lankes HA, Ramirez NC, King MC, **Birrer MJ**, Swisher EM. Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study. *Clin Cancer Res*. 2018 Feb 15;24(4):777-783. doi: 10.1158/1078-0432.CCR-17-1327. Epub 2017 Nov 30. PMID: 29191972
336. Moore KN, **Birrer MJ**. Administration of the Tablet Formulation of Olaparib in Patients with Ovarian Cancer: Practical Guidance and Expectations. *Oncologist*. 2018 Mar 28. pii:

theoncologist.2017-0485. doi: 10.1634/theoncologist.2017-0485. [Epub ahead of print] Review. PMID: 29593098

337. Caumanns JJ, Berns K, Wisman GBA, Fehrmann RSN, Tomar T, Klip H, Meersma GJ, Hijmans EM, Gennissen A, Duiker EW, Weening D, Itamochi H, Kluin RJ, Reyners AKL, **Birrer MJ**, Salvesen HB, Vergote I, Van Nieuwenhuysen E, Brenton JD, Braicu EI, Kupryjanczyk J, Spiewankiewicz B, Mittempergher L, Bernards R, van der Zee AGJ, de Jong S. Integrative kinome profiling identifies mTORC1/2 inhibition as treatment strategy in ovarian clear cell carcinoma. *Clin Cancer Res*. 2018 Apr 23. pii: clincanres.3060.2017. doi: 10.1158/1078-0432.CCR-17-3060. [Epub ahead of print] PMID: 29685880
338. Moore KN, O'Malley DM, Vergote I, Martin LP, Gonzalez-Martin A, Malek K, **Birrer MJ**. Safety and activity findings from a phase 1b escalation study of mirvetuximab soravtansine, a folate receptor alpha (FR α)-targeting antibody-drug conjugate (ADC), in combination with carboplatin in patients with platinum-sensitive ovarian cancer. *Gynecol Oncol*. 2018 Oct; 151(1):46-52. doi: 10.1016/j.ygyno.2018.07.017. Epub 2018 Aug 6. PMID: 30093227
339. Matulonis UA, **Birrer MJ**, O'Malley DM, Moore KN, Konner J, Gilbert L, Martin LP, Bauer TM, Oza AM, Malek K, Pinkas J, Kim SK. Evaluation of Prophylactic Corticosteroid Eye Drop Use in the Management of Corneal Abnormalities Induced by the Antibody-Drug Conjugate Mirvetuximab Soravtansine. *Clin Cancer Res*. 2018 Nov 9. doi: 10.1158/1078-0432.CCR-18-2474. [Epub ahead of print] PMID: 30413525
340. Yeung TL, Tsai CC, Leung CS, Au Yeung CL, Thompson MS, Lu KH, Freedman RS, **Birrer MJ**, Wong KK, Mok SC. ISG15 Promotes ERK1 ISGylation, CD8+ T Cell Activation and Suppresses Ovarian Cancer Progression. *Cancers (Basel)*. 2018 Nov 22;10(12). pii: E464. doi: 10.3390/cancers10120464. PMID: 30469497. PMCID: PMC6316352.
341. Rauh-Hain JA, Hidrue MK, Gaccione P, Melamed A, Meyer LA, Keating NL, Giordano SH, Rice LW, **Birrer MJ**, Del Carmen MG. Variation in resource utilization associated with the surgical management of ovarian cancer. *Gynecol Oncol*. 2018 Dec 19. pii: S0090-8258(18)31513-0. doi: 10.1016/j.ygyno.2018.12.013. [Epub ahead of print] PMID: 30579568.
342. **Birrer MJ**, Betella I, Martin LP, Moore KN. Is Targeting the Folate Receptor in Ovarian Cancer Coming of Age? *Oncologist*. 2019 Jan 11. pii: theoncologist.2018-0459. doi: 10.1634/theoncologist.2018-0459. [Epub ahead of print] No abstract available. PMID: 30635448

BOOKS AND BOOK CHAPTERS

1. Minna JD, Battey JF, **Birrer MJ**, Cuttitta F, DeGreve J, Gazdar AF, Ihde DC, Johnson BE, Kaye F, Krystal GW, Lebacqz AM, Linnoila IR, Mulshine J, Nau MM, Sausville EA, Schutte T, Trepel JB. Genetic changes involved in the pathogenesis of human lung cancer including oncogene activation, chromosomal deletions, and autocrine growth factor production. In: Fortner JG, Rhoads JE, editors. *Accomplishments in cancer research*. Philadelphia: JB Lippincott, 1988. p. 155-182.
2. Minna JD, Kaye FJ, Takahashi T, Harbour JW, Rosenberg R, Nau M, Whang-Peng J, Johnson B,

- Birrer MJ**, Gazdar AF. Recessive oncogenes and chromosomal deletions in human lung cancer. In: Cavennee W, Hastie N, Stanbridge E, editors. Recessive oncogenes and tumor suppression. Cold Spring Harbor Laboratory, 1989, p. 57-65.
3. Brown PH, Mulshine J, and **Birrer MJ**. Tumor initiators and promoters in lung cancer. Lung Cancer Research Quarterly 1:3-16, 1991.
 4. Siegfried JM, **Birrer MJ**, and Cuttitta F. Detection of growth factor effects and expression in normal and neoplastic human bronchial epithelial cell. In: Milo G.E., et al. editors. Transformation of Human Epithelial Cells: Molecular Oncogenetic Mechanisms. Boca Raton: CRC, 1992.
 5. Mulshine JL, **Birrer MJ**, Treston AM, Scott F, Quinn K, Avis I, and Cuttitta F: Growth factors and targets for rational application intervention agents. In: Newell GR, Hong WK, editors. The Biology and Prevention of Aerodigestive Tract Cancers. New York: Plenum, 1992. p. 81-88.
 6. Mulshine JL, Shaw GL, Cuttitta F, Scott F, Avis I, Treston AM, Linnoila RI, **Birrer MJ**, Brown P, Gupta PK, and Tockman MS: Applications of biomarkers for lung cancer early detection. In Fortner JG, Rhoads JE, editors. Accomplishments in cancer research. Philadelphia: JB Lippincott, 1992. p. 204-218.
 7. Draoui M, Battey J, **Birrer MJ**, Moody TW. Regulation of gastrin releasing peptide gene expression. In: Moody TW, editor. Growth Factors, Peptides, and Receptors. New York: Plenum, 1993. p. 347-352.
 8. Teneriello MG, Hall KL, Lemon SJ, Nash JD, **Birrer MJ**. Genetic alterations in gynecologic cancers. In: Srivastava S, Lippman SM, Hong WK, Mulshine, JL, editors. Early Detection of Cancer: Molecular Markers. Armonk, New York: Futura Publishing, 1994. p. 97-119.
 9. **Birrer MJ**, Gray JW, Lippman SM, Lubet R, Mulshine JL, Shaw GL, Srivastava S, and Tockman S. Basic science, technical development, and clinical and laboratory-to-field application issues. In: Srivastava S, Lippman SM, Hong WK, Mulshine JL, editors. Early Detection of Cancer: Molecular Markers. Armonk, New York: Futura, 1994. p. 289-308.
 10. Szabo E, **Birrer MJ**. Oncogenes, cancer and growth factors. In: Barnes PJ and Stockley RA, editors. Molecular biology of lung diseases. Oxford: Blackwell Scientific, 1994. p. 173-191.
 11. Lemon SJ, Sabichi AL, and **Birrer MJ**. Genetic alterations in lung cancer. In: Garrett CT and Sells S, editors. Cellular Cancer Markers. Totowa: Humana, 1995. p. 209-231.
 12. Sabichi AL, Bober MA, and **Birrer MJ**. Lung cancer. In Kurzrock R and Talpaz M, editors. Molecular biology in cancer medicine. London: Martin Dunitz, 1995. p. 223-241.
 13. Parker MF, Sausville EA, **Birrer MJ**. Basic biology and biochemistry of gynecologic cancer. In: Hoskins W, Perez CA, Young RC, editors. Principles and practice of gynecology oncology, 2nd edition. Philadelphia: Lippincott-Raven, 1997, p. 61-86.

14. Farley J, Hendricks D, **Birrer MJ**. Ovarian and endometrial cancer molecular pathology. In: Srivastava S, Henson DE, and Gazdar A, editors. Molecular pathology of early cancer. Amsterdam, IOS, 1998, p.21-34.
15. Rose GS, Carlson J, and **Birrer MJ**. Basic biology and biochemistry of gynecologic cancer. In: Hoskins, W, Perez, CA, and Young, RC, editors. Principles and practice of gynecology oncology, 2nd ed. Philadelphia: Lippincott-Raven, 2000. p. 62-85.
16. Zorn K, Gardner G, **Birrer MJ**. Basic biology of gynecologic cancer. In: Hoskins W, Perez CA, Young RC, editors. Principles and practice of gynecology oncology, 3rd edition. Philadelphia: Lippincott-Raven, 2004.
17. Zorn KK, Gardner GJ, **Birrer MJ**. Epithelial ovarian Cancer. In: Kelloff GJ, Hawk ET, Sigman CC, editors. Cancer Chemoprevention Volume 2: Strategies for cancer chemoprevention. Totowa, Humana Press Inc, 2005. p. 473-489.
18. Annunziata CM, and **Birrer, MJ**. Endometrial Cancer. In: Abraham J, Allegra CJ, Gulley J, editors. Bethesda Handbook of Clinical Oncology, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2005. p. 237-245.
19. Annunziata CM, and **Birrer, MJ**. Vulvar Cancer. In: Abraham J, Allegra CJ, Gulley J, editors. Bethesda. Handbook of Clinical Oncology, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2005. p. 257-265.
20. Zorn K, Gardner G; Farley J, and **Birrer, MJ**. Basic biology of gynecologic cancer. In: Hoskins W, Perez CA, Young RC, editors. Principles and practice of gynecology oncology, 4th edition. Philadelphia, Lippincott-Raven, 2007.
21. **Birrer MJ**, Zorn, KK, Gardner, GJ. Molecular profiling in ovarian cancer. In: Levenback CF, Sood, AK, Lu KH, Coleman RL, editors. Prognostic and predictive factors in gynecologic cancers. London, UK: Informa Ltd, 2007.
22. Farley J, Ozbun, LL, **Birrer MJ**. Whole-genome expression profiling of papillary serous ovarian cancer: Activted pathways, potential targets and noise. In: Yuryev A, editor. A pathway analysis for drug discovery. Hoboken, NJ: John Wiley & Sons, Inc., 2008.
23. Stany M, Farley J, **Birrer MJ**. Chemotherapy: principles and practice. In: Fishman D, editor. Gynecologic oncology. Requisites in obstetrics and gynecology, Philadelphia: Elsevier-Global Medicine, 2008.
24. Farley J, **Birrer MJ**. Novel therapeutic targets. In: Stack MS, Fishman DA, editors. Ovarian cancer, 2nd edition. Springer Science Business Media, LLS, 2009. p. 63-84.
25. Annunziata CM, **Birrer MJ**. Vulvar cancer. In: Abraham J, Allegra C, Gulley J, editors. Bethesda Manual of Clinical Oncology. Philadelphia: Lippincott, Williams and Wilkins, 2008. p. 257-264. (3rd ed. 2010, p. 252-260)

26. Annunziata CM, **Birrer MJ**. Endometrial Carcinoma. In: Abraham J, Allegra C, Gulley J, editors. Bethesda Manual of Clinical Oncology. Philadelphia: Lippincott, Williams and Wilkins, 2008, p. 237-244. (3rd ed. 2010, p. 233-240)
27. McNally T, Penson R, Tran C, **Birrer MJ**. Gynecologic Cancer. In: Skeel RT, Khlief SN, editors. Handbook of Cancer Chemotherapy. 8th Edition. Philadelphia: Lippincott, Williams and Wilkins, 2011. p. 199-232.
28. Pejovic T, **Birrer MJ**, Anderson ML, Odunsi K. Molecular biology of gynecologic cancers. In: DeVita VT, Lawrence TS, Rosenberg SA, editors. Cancer: Principles and practice of oncology. 10th edition. Philadelphia: Lippincott, Williams and Wilkins, Jan 2015. p. 1005-1012.
29. del Carmen MG, Young RH, Schorge JO, **Birrer MJ**, editors. Uncommon Gynecologic Cancers. John Wiley & Sons, Ltd., 2015
30. **Birrer M**, Ceppi L, editors. Translational Advances in Gynecologic Cancers. Elsevier, 2017.

PUBLISHED ABSTRACTS - Greater than 500 published abstracts

APPENDIX B

Fed. R. Civ. P. 26(a)(2)(B)(v) Disclosure for Michael Birrer, MD, PhD
(As of Feb. 2019)

Depositions

- *Blaes v. Johnson & Johnson*, No. 1422-CC09326-01 (Mo. Cir. Ct. deposed June 8-9, 2017)
- *Brower v. Johnson & Johnson*, No. 16-EV-005534 (Ga. Fulton Cnty. deposed Sept. 25, 2018)

Exhibit I

IARC MONOGRAPHS

ARSENIC, METALS, FIBRES, AND DUSTS

**VOLUME 100 C
A REVIEW OF HUMAN CARCINOGENS**

**IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS**

International Agency for Research on Cancer



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physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as ‘weak’, ‘moderate’ or ‘strong’. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources

have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental

animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity*

in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) *Rationale*

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

References

- Bieler GS & Williams RL (1993). Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*, 49: 793–801. doi:10.2307/2532200 PMID:8241374
- Breslow NE & Day NE (1980). Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ*, 32: 5–338. PMID:7216345
- Breslow NE & Day NE (1987). Statistical methods in cancer research. Volume II—The design and analysis of cohort studies. *IARC Sci Publ*, 82: 1–406. PMID:3329634
- Buffler P, Rice J, Baan R *et al.* (2004). Workshop on Mechanisms of Carcinogenesis: Contributions of Molecular Epidemiology. Lyon, 14–17 November 2001. Workshop report. *IARC Sci Publ*, 157: 1–27. PMID:15055286
- Capen CC, Dybing E, Rice JM, Wilbourn JD (1999). Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis. Proceedings of a consensus conference. Lyon, France, 3–7 November 1997. *IARC Sci Publ*, 147: 1–225.
- Cogliano V, Baan R, Straif K *et al.* (2005). Transparency in IARC Monographs. *Lancet Oncol*, 6: 747. doi:10.1016/S1470-2045(05)70380-6
- Cogliano VJ, Baan RA, Straif K *et al.* (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect*, 112: 1269–1274. doi:10.1289/ehp.6950 PMID:15345338
- Dunson DB, Chen Z, Harry J (2003). A Bayesian approach for joint modeling of cluster size and subunit-specific outcomes. *Biometrics*, 59: 521–530. doi:10.1111/1541-0420.00062 PMID:14601753
- Fung KY, Krewski D, Smythe RT (1996). A comparison of tests for trend with historical controls in carcinogen bioassay. *Can J Stat*, 24: 431–454. doi:10.2307/3315326
- Gart JJ, Krewski D, Lee PN *et al.* (1986). Statistical methods in cancer research. Volume III—The design and analysis of long-term animal experiments. *IARC Sci Publ*, 79: 1–219. PMID:3301661
- Greenland S (1998). Meta-analysis. In: *Modern Epidemiology*. Rothman KJ, Greenland S, editors. Philadelphia: Lippincott Williams & Wilkins, pp. 643–673
- Greim H, Gelbke H-P, Reuter U *et al.* (2003). Evaluation of historical control data in carcinogenicity studies. *Hum Exp Toxicol*, 22: 541–549. doi:10.1191/0960327103ht3940a PMID:14655720
- Haseman JK, Huff J, Boorman GA (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol Pathol*, 12: 126–135. doi:10.1177/019262338401200203 PMID:11478313
- Hill AB (1965). The environment and disease: Association or causation? *Proc R Soc Med*, 58: 295–300. PMID:14283879
- Hoel DG, Kaplan NL, Anderson MW (1983). Implication of nonlinear kinetics on risk estimation in carcinogenesis. *Science*, 219: 1032–1037. doi:10.1126/science.6823565 PMID:6823565
- Huff JE, Eustis SL, Haseman JK (1989). Occurrence and relevance of chemically induced benign neoplasms in long-term carcinogenicity studies. *Cancer Metastasis Rev*, 8: 1–22. doi:10.1007/BF00047055 PMID:2667783
- IARC (1977). *IARC Monographs Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Preamble (IARC Intern Tech Rep No. 77/002)
- IARC (1978). *Chemicals with Sufficient Evidence of Carcinogenicity in Experimental Animals* – IARC Monographs Volumes 1–17 (IARC Intern Tech Rep No. 78/003)

IARC MONOGRAPHS – 100C

- IARC (1979). *Criteria to Select Chemicals for IARC Monographs* (IARC Intern Tech Rep No. 79/003)
- IARC (1982). Chemicals, industrial processes and industries associated with cancer in humans (IARC Monographs, Volumes 1 to 29). *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 4: 1–292.
- IARC (1983). *Approaches to Classifying Chemical Carcinogens According to Mechanism of Action* (IARC Intern Tech Rep No. 83/001)
- IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203
- IARC (1988). *Report of an IARC Working Group to Review the Approaches and Processes Used to Evaluate the Carcinogenicity of Mixtures and Groups of Chemicals* (IARC Intern Tech Rep No. 88/002)
- IARC (1991). *A Consensus Report of an IARC Monographs Working Group on the Use of Mechanisms of Carcinogenesis in Risk Identification* (IARC Intern Tech Rep No. 91/002)
- IARC (2005). *Report of the Advisory Group to Recommend Updates to the Preamble to the IARC Monographs* (IARC Intern Rep No. 05/001)
- IARC (2006). *Report of the Advisory Group to Review the Amended Preamble to the IARC Monographs* (IARC Intern Rep No. 06/001)
- IARC (2004). Some drinking-water disinfectants and contaminants, including arsenic. *IARC Monogr Eval Carcinog Risks Hum*, 84: 1–477. PMID:15645577
- McGregor DB, Rice JM, Venitt S, editors (1999). The use of short- and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation. Consensus report. *IARC Sci Publ*, 146: 1–536.
- Montesano R, Bartsch H, Vainio H *et al.*, editors (1986). Long-term and short-term assays for carcinogenesis—a critical appraisal. *IARC Sci Publ*, 83: 1–564.
- OECD (2002). *Guidance Notes for Analysis and Evaluation of Chronic Toxicity and Carcinogenicity Studies* (Series on Testing and Assessment No. 35), Paris: OECD
- Peto R, Pike MC, Day NE *et al.* (1980). Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 2: 311–426. PMID:6935185
- Portier CJ & Bailer AJ (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol*, 12: 731–737. doi:10.1016/0272-0590(89)90004-3 PMID:2744275
- Sherman CD, Portier CJ, Kopp-Schneider A (1994). Multistage models of carcinogenesis: an approximation for the size and number distribution of late-stage clones. *Risk Anal*, 14: 1039–1048. doi:10.1111/j.1539-6924.1994.tb00074.x PMID:7846311
- Stewart BW, Kleihues P, editors (2003). *World Cancer Report*, Lyon: IARC
- Tomatis L, Aitio A, Wilbourn J, Shuker L (1989). Human carcinogens so far identified. *Jpn J Cancer Res*, 80: 795–807. PMID:2513295
- Toniolo P, Boffetta P, Shuker DEG *et al.*, editors (1997). Proceedings of the workshop on application of biomarkers to cancer epidemiology. Lyon, France, 20–23 February 1996. *IARC Sci Publ*, 142: 1–318.
- Vainio H, Magee P, McGregor D, McMichael A, editors (1992). Mechanisms of carcinogenesis in risk identification. IARC Working Group Meeting. Lyon, 11–18 June 1991. *IARC Sci Publ*, 116: 1–608.
- Vainio H, Wilbourn JD, Saso AJ *et al.* (1995). [Identification of human carcinogenic risks in IARC monographs.] *Bull Cancer*, 82: 339–348. PMID:7626841
- Vineis P, Malats N, Lang M *et al.*, editors (1999). Metabolic Polymorphisms and Susceptibility to Cancer. *IARC Sci Publ*, 148: 1–510. PMID:10493243
- Wilbourn J, Haroun L, Heseltine E *et al.* (1986). Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs programme. *Carcinogenesis*, 7: 1853–1863. doi:10.1093/carcin/7.11.1853 PMID:3769134

CHROMIUM (VI) COMPOUNDS

Chromium (VI) compounds were considered by previous IARC Working Groups in 1972, 1979, 1982, 1987, and 1989 ([IARC, 1973, 1979, 1980, 1982, 1987, 1990](#)). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for selected chromium (VI) compounds are presented in [Table 1.1](#). This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various chromium-containing substances. Rather, it is indicative of the range of chromium (VI) compounds available.

1.2 Chemical and physical properties of the agents

Chromium (VI), also known as hexavalent chromium, is the second most stable oxidation state of chromium. Rarely occurring naturally, most chromium (VI) compounds are manufactured (products or by-products). Chromium (VI) can be reduced to the more stable chromium (III) in the presence of reducing agents (e.g. iron) or oxidizable organic matter ([OSHA, 2006](#)). Selected chemical and physical properties of various chromium (VI) compounds are presented in the previous *IARC Monograph* ([IARC, 1990](#)).

Chromium (VI) compounds are customarily classed as soluble or insoluble in water. Examples of water-soluble chromium (VI) compounds are sodium chromate (873 g/L at 30 °C) and potassium chromate (629 g/L at 20 °C). Water-insoluble chromium (VI) compounds include barium chromate (2.6 mg/L at 20 °C), and lead chromate (0.17 mg/L at 20 °C) ([Lide, 2008](#)). Compounds with solubilities in the middle of this range are not easily classified, and technical-grade compounds, such as the various zinc chromates, can have a wide range of solubilities ([IARC, 1990](#)). In the United States of America, the Occupational Safety and Health Administration (OSHA) has divided chromium (VI) compounds and mixtures into the following three categories: water-insoluble (solubility < 0.01 g/L), slightly soluble (solubility 0.01 g/L–500 g/L), and, highly water-soluble (solubility ≥ 500 g/L) ([OSHA, 2006](#)).

Chromium (VI) compounds are mostly lemon-yellow to orange to dark red in colour. They are typically solid (i.e. crystalline, granular, or powdery) although one compound (chromyl chloride) is a dark red liquid that decomposes into chromate ion and hydrochloric acid in water ([OSHA, 2006](#)).

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Table 1.1 Chemical names (CAS names are given in *italics*), synonyms, and molecular formulae of selected chromium (VI) compounds

Chemical name	CAS No. ^a	Synonyms	Formula ^b
Ammonium chromate	7788-98-9	Chromic acid, ammonium salt; <i>chromic acid</i> (H_2CrO_4), <i>diammonium salt</i> ; diammonium chromate	$(NH_4)_2CrO_4$
Ammonium dichromate	7789-09-5	Ammonium bichromate; ammonium chromate; <i>chromic acid</i> ($H_2Cr_2O_7$), <i>diammonium salt</i> ; diammonium dichromate; dichromic acid, diammonium salt	$(NH_4)_2Cr_2O_7$
Barium chromate	10294-40-3 (12000-34-9; 12 231-18-4)	Barium chromate (VI); barium chromate (1:1); barium chromate oxide; <i>chromic acid</i> (H_2CrO_4), <i>barium salt</i> (1:1)	$BaCrO_4$
Basic lead chromate	1344-38-3 (54692-53-4)	C.I. 77 601; C.I. <i>Pigment Orange 21</i> ; C.I. <i>Pigment Red</i> ; lead chromate oxide	$PbO \cdot PbCrO_4$
Calcium chromate	13765-19-0	Calcium chromium oxide; calcium monochromate; <i>chromic acid</i> (H_2CrO_4), <i>calcium salt</i> (1:1); C.I. 77223; C.I. <i>Pigment Yellow 33</i>	$CaCrO_4$
Chromium [VI] chloride	14986-48-2	Chromium hexachloride; (OC-6-11)- <i>chromium chloride</i> ($CrCl_6$)	$CrCl_6$
Chromium trioxide	1333-82-0 (12324-05-9; 12324-08-2)	Chromia; chromic acid; chromic (VI) acid; chromic acid, solid; chromic anhydride; chromic trioxide; <i>chromium oxide</i> (CrO_3); chromium (VI) oxide; chromium (6+) trioxide; monochromium trioxide	CrO_3
Chromyl chloride	14977-61-8	Chlorochromic anhydride; chromium chloride oxide; chromium dichloride dioxide; <i>chromium, dichlorodioxo-</i> (T-4); chromium dioxide dichloride; chromium dioxychloride; chromium oxychloride; dichlorodioxochromium	CrO_2Cl_2
Lead chromate	7758-97-6 (8049-64-7) 1344-37-2	<i>Chromic acid</i> (H_2CrO_4), <i>lead</i> (2+) <i>salt</i> (1:1); C.I. 77600; C.I. <i>Pigment Yellow 34</i> ; Chrome Yellow; lead chromate/lead sulfate mixture	$PbCrO_4$
Molybdenum orange	12656-85-8	C.I. <i>Pigment Red 104</i> ; lead chromate molybdate sulfate red	$PbMoO_4$ $PbCrO_4$ $PbSO_4$
Potassium chromate	7789-00-6	Bipotassium chromate; <i>chromic acid</i> (H_2CrO_4), <i>dipotassium salt</i> ; dipotassium chromate; dipotassium monochromate; neutral potassium chromate; potassium chromate (VI)	K_2CrO_4
Potassium dichromate	7778-50-9	<i>Chromic acid</i> ($H_2Cr_2O_7$), <i>dipotassium salt</i> ; dichromic acid, dipotassium salt; dipotassium bichromate; dipotassium dichromate; potassium bichromate; potassium dichromate (VI)	$K_2Cr_2O_7$
Sodium chromate	7775-11-3	<i>Chromic acid</i> (H_2CrO_4), <i>disodium salt</i> ; chromium disodium oxide; chromium sodium oxide; disodium chromate; neutral sodium chromate; sodium chromium oxide	Na_2CrO_4

Chromium (VI) compounds

Table 1.1 (continued)

Chemical name	CAS No. ^a	Synonyms	Formula ^b
Sodium dichromate	10588-01-9 (12018-32-5)	Bichromate of soda; <i>chromic acid</i> ($H_2Cr_2O_7$), <i>disodium salt</i> ; chromium sodium oxide; dichromic acid, disodium salt; disodium dichromate; sodium bichromate; sodium dichromate (VI)	$Na_2Cr_2O_7$
Strontium chromate	7789-06-2 (54322-60-0)	<i>Chromic acid</i> (H_2CrO_4), <i>strontium salt</i> (1:1); C.I. Pigment Yellow 32; strontium chromate (VI); strontium chromate (1:1)	$SrCrO_4$
Zinc chromate ^c	13530-65-9 (1308-13-0; 1328-67-2; 14675-41-3)	<i>Chromic acid</i> (H_2CrO_4), <i>zinc salt</i> (1:1); chromium zinc oxide; zinc chromium oxide; zinc tetraoxochromate; zinc tetroxychromate	$ZnCrO_4$
Zinc chromate hydroxides	15930-94-6 (12206-12-1; 66516-58-3)	Basic zinc chromate; chromic acid (H_6CrO_9), zinc salt (1:2); chromic acid (H_4CrO_5), zinc salt (1:2), monohydrate; chromium zinc hydroxide oxide; zinc chromate hydroxide; zinc chromate (VI) hydroxide; <i>zinc chromate oxide</i> ($Zn_2(CrO_4)O$), <i>monohydrate</i> ; zinc hydroxychromate; zinc tetrahydroxychromate; zinc yellow ^d	$Zn_2CrO_4(OH)_2$ and others
Zinc potassium chromates (hydroxides)	11103-86-9 (12527-08-1; 37809-34-0)	Basic zinc potassium chromate; chromic acid ($H_6Cr_2O_9$), potassium zinc salt (1:1:2); <i>potassium hydroxyoctaoxodizincate dichromate</i> (1-); potassium zinc chromate hydroxide; zinc yellow ^d	$KZn_2(CrO_4)_2(OH)$ and others

^a Replaced CAS Registry numbers are given in parentheses.^b Compounds with the same synonym or trade name can have different formulae.^c The term 'zinc chromate' is also used to refer to a wide range of commercial zinc and zinc potassium chromates.^d 'Zinc yellow' can refer to several zinc chromate pigments; it has the CAS No. 37300-23-5.

1.3 Use of the agents

Chromium (VI) compounds are used widely in applications that include: pigment for textile dyes (e.g. ammonium dichromate, potassium chromate, sodium chromate), as well as for paints, inks, and plastics (e.g. lead chromate, zinc chromate, barium chromate, calcium chromate, potassium dichromate, sodium chromate); corrosion inhibitors (chromic trioxide, zinc chromate, barium chromate, calcium chromate, sodium chromate, strontium chromate); wood preservatives (chromium trioxide); metal finishing and chrome plating (chromium trioxide, strontium chromate), and leather tanning (ammonium dichromate). Chromium (VI) may be present as an impurity in Portland cement, and it can be generated and given off during casting, welding, and cutting operations (for example, of stainless steel), even if it was not originally present in its hexavalent state ([NTP, 2005](#); [OHCOW, 2005](#); [OSHA, 2006](#)).

1.4 Environmental occurrence

Chromium (VI) can occur naturally in the earth's crust, although it is primarily emitted to the environment as a result of anthropogenic activities. The occurrence and distribution of chromium in the environment has been extensively reviewed ([Mukherjee, 1998](#); [Kotaś & Stasicka, 2000](#); [Rowbotham et al., 2000](#); [Ellis et al., 2002](#); [Paustenbach et al., 2003](#); [Guertin et al., 2004](#); [Reinds et al., 2006](#); [Krystek & Ritsema, 2007](#)).

1.4.1 Natural occurrence

Only lead chromate (as crocoite) and potassium dichromate (as lopezite) are known to occur in nature ([IARC, 1990](#)).

1.4.2 Air

Chromium (VI) is reported to account for approximately one third of the 2700–2900 tons of chromium emitted to the atmosphere annually in the USA ([ATSDR, 2008a](#)). Based on US data collected from 2106 monitoring stations during 1977–84, the arithmetic mean concentrations of total chromium in the ambient air (urban, suburban, and rural) were in the range of 0.005–0.525 µg/m³ ([ATSDR, 2000](#)).

1.4.3 Water

The concentration of chromium in uncontaminated waters is extremely low (< 1 µg/L or < 0.02 µmol/L). Anthropogenic activities (e.g. electroplating, leather tanning) and leaching of wastewater (e.g. from sites such as landfills) may cause contamination of the drinking-water ([EVM, 2002](#)). Chromium (VI) has been identified in surface water ($n = 32$) and groundwater samples ($n = 113$) collected from 120 hazardous waste sites in the USA ([ATSDR, 2000](#)), and 38% of municipal sources of drinking-water in California, USA, reportedly have levels of chromium (VI) greater than the detection limit of 1 µg/L ([Sedman et al., 2006](#)).

1.4.4 Soil

Chromium is present in most soils in its trivalent form, although chromium (VI) can occur under oxidizing conditions ([ATSDR, 2008a](#)). In the USA, the geometric mean concentration of total chromium was 37.0 mg/kg (range, 1.0–2000 mg/kg) based on 1319 samples collected in coterminous soils ([ATSDR, 2000](#)).

1.4.5 Food

There is little information available on chromium (VI) in food. Most of the chromium ingested with food is chromium (III) ([EVM, 2002](#)).

1.4.6 Smoking

Tobacco smoke contains chromium (VI), and indoor air polluted by cigarette smoke can contain hundreds of times the amount of chromium (VI) found in outdoor air.

1.5 Human exposure

1.5.1 Exposure of the general population

The general population residing in the vicinity of anthropogenic sources of chromium (VI) may be exposed through inhalation of ambient air or ingestion of contaminated drinking-water ([ATSDR, 2000](#)).

1.5.2 Occupational exposure

Inhalation of dusts, mists or fumes, and dermal contact with chromium-containing products are the main routes of occupational exposure. Industries and processes in which exposure to chromium (VI) occurs include: production, use and welding of chromium-containing metals and alloys (e.g. stainless steels, high-chromium steels); electroplating; production and use of chromium-containing compounds, such as pigments, paints (e.g. application in the aerospace industry and removal in construction and maritime industries), catalysts, chromic acid, tanning agents, and pesticides ([OSHA, 2006](#)).

Occupational exposures to several specific chromium compounds are reported in the previous *IARC Monograph* ([IARC, 1990](#)). With respect to chromium (VI) compounds, the most important exposures have been to sodium, potassium, calcium, and ammonium chromates and dichromates during chromate production; to chromium trioxide during chrome plating; to insoluble chromates of zinc and lead during pigment production and spray painting; to water-soluble alkaline chromates during steel smelting and welding; and, to other chromates during cement production and use (see Table 10; [IARC,](#)

[1990](#), and [OHCOW, 2005](#)) for lists of occupations potentially exposed to chromium (VI)).

Estimates of the number of workers potentially exposed to chromium (VI) compounds have been developed by CAREX (CARcinogen EXposure) in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that 785692 workers were exposed to hexavalent chromium compounds in the European Union, with over 58% of workers employed in the following four industries: manufacture of fabricated metal products except machinery and equipment ($n = 178329$), manufacture of machinery except electrical ($n = 114452$), personal and household services ($n = 85616$), and manufacture of transport equipment ($n = 82359$). [CAREX Canada \(2011\)](#) estimates that 83000 Canadians are occupationally exposed to chromium (VI) compounds. Industries in which exposure occurred include: printing and support activities; architectural/structure metal manufacturing; agricultural, construction, mining machinery manufacturing; specialty trade contractors; boiler, tank, and container manufacturing; industrial machinery repair; auto repair; metalworking machinery manufacturing; steel product manufacturing; aluminum production; metal ore mining; coating, engraving, and heat treating. Welders were the largest occupational group exposed ($n = 19100$ men and 750 women).

Data on early occupational exposures to chromium (VI) are summarized in the previous *IARC Monograph* ([IARC, 1990](#)). Data from studies on chromium (VI) exposure published since the previous *IARC Monograph* are summarized below.

In a study to characterize occupational exposure to airborne particulate containing chromium, and to evaluate existing control technologies, the US National Institute for Occupational Safety and Health (NIOSH) conducted 21 field surveys during 1999–2001 in selected industries. Industries and operations

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evaluated included: chromium electroplating facilities; welding in construction; metal cutting operations on chromium-containing materials in ship breaking; chromate-paint removal with abrasive blasting; atomized alloy-spray coating; foundry operations; printing; and the manufacture of refractory brick, coloured glass, prefabricated concrete products, and treated wood products. Personal breathing zone samples (full-shift and short-term) and general area samples were collected. Results were compared to the NIOSH recommended exposure limit (REL) of $1 \mu\text{g}/\text{m}^3$ (for a 10-hour exposure). Full-shift personal exposures to chromium (VI) were in the range of $3.0\text{--}16 \mu\text{g}/\text{m}^3$ at the electroplating facilities, and $2.4\text{--}55 \mu\text{g}/\text{m}^3$ at a painting and coating facility that used products containing chromium (VI) ([Blade et al., 2007](#)).

NIOSH conducted a health hazard evaluation of worker exposures during the welding and manufacturing of stainless steel products and fabricated piping systems. Personal breathing zone air sampling concentrations of chromium (VI) were above the NIOSH REL. The highest concentrations for nickel and chromium (VI) occurred during welding operations inside large stainless steel pipes ($0.26 \text{ mg}/\text{m}^3$ and $0.36 \text{ mg}/\text{m}^3$), and while welding fins on a large stainless steel pipe ([Hall et al., 2005](#)).

As part of an international epidemiological study of workers in the pulp and paper industry, [Teschke et al. \(1999\)](#) assembled and analysed 7293 previously unpublished exposure measurements collected in non-production departments from 147 mills in 11 countries. Chromium (VI) compounds were reported in 26 time-weighted average (TWA) samples from nine mills, with a mean airborne chromium (VI) concentration of $63 \mu\text{g}/\text{m}^3$ (range, $0.04\text{--}1220 \mu\text{g}/\text{m}^3$).

[Proctor et al. \(2003\)](#) analysed more than 800 measurements of airborne chromium (VI) from 23 surveys conducted during 1943–71 at a chromate production plant in Painesville, Ohio, USA. The highest chromium (VI) concentrations

recorded at the plant occurred in shipping (e.g. bagging of dichromate), lime and ash, and filtering operations (maximum yearly TWA concentrations of 8.9 , 2.7 , and $2.3 \text{ mg}/\text{m}^3$, respectively). The data showed that concentrations in the indoor operating areas of the plant generally decreased over time, dropping from $0.72 \text{ mg}/\text{m}^3$ in the 1940s, to $0.27 \text{ mg}/\text{m}^3$ in 1957–64, and to $0.039 \text{ mg}/\text{m}^3$ in 1965–72.

In a study to assess industry compliance with existing and proposed standards, [Lurie & Wolfe \(2002\)](#) conducted a secondary data analysis of 813 chromium (VI) measurements collected in 1990–2000 by OSHA. Chromium (VI) was not detected in 436 measurements. In the remaining samples, the median 8-hour TWA concentration was $10 \text{ mg}/\text{m}^3$ ($n = 197$; range, $0.01\text{--}13960 \text{ mg}/\text{m}^3$), and the median ceiling concentration was $40.5 \text{ mg}/\text{m}^3$ ($n = 180$; range, $0.25\text{--}25000 \text{ mg}/\text{m}^3$). In the plating and polishing industry, the median 8-hour TWA concentration was $8.2 \text{ mg}/\text{m}^3$ ($n = 65$; range, $0.01\text{--}400 \text{ mg}/\text{m}^3$), and the median ceiling concentration was $23 \text{ mg}/\text{m}^3$ ($n = 51$; range, $1\text{--}410 \text{ mg}/\text{m}^3$).

[Luippold et al. \(2005\)](#) examined the mortality of two cohorts of chromate production workers constituting the current US chromium chemical industry, after engineering controls were implemented. Personal air monitoring sampling for chromium (VI) at the two plants resulted in approximately 5230 personal air-monitoring measurements taken during 1974–88 for Plant 1, and 1200 measurements taken during 1981–98 for Plant 2. Personal levels of chromium (VI) exposure were very low at both plants (geometric mean, $< 1.5 \mu\text{g}/\text{m}^3$ for most years; range of annual means, $0.36\text{--}4.36 \mu\text{g}/\text{m}^3$). At both plants, the work areas with the highest average exposures were generally less than $10 \mu\text{g}/\text{m}^3$ for most years.

In an occupational exposure study of chromium in an aircraft construction factory, personal airborne samples were collected in a group of 16 workers over a 4-hour period, and urinary samples were collected from 55

workers at the beginning of their work shift (on Monday), and at the beginning and end of their work shift (on Friday). The geometric mean air concentration was $0.17 \mu\text{g}/\text{m}^3$ (GSD, $5.35 \mu\text{g}/\text{m}^3$; range, $0.02\text{--}1.5 \mu\text{g}/\text{m}^3$). Geometric mean creatinine levels were as follows: pre-shift Monday, $0.63 \mu\text{g}/\text{g}$ (GSD, $0.53 \mu\text{g}/\text{g}$; range, $0.23\text{--}2.9 \mu\text{g}/\text{g}$); pre-shift Friday, $0.95 \mu\text{g}/\text{g}$ (GSD, $0.94 \mu\text{g}/\text{g}$; range, $0.25\text{--}4.8 \mu\text{g}/\text{g}$); and post-shift Friday, $0.91 \mu\text{g}/\text{g}$ (GSD, $1.38 \mu\text{g}/\text{g}$; range, $0.16\text{--}7.7 \mu\text{g}/\text{g}$) ([Gianello et al., 1998](#)).

2. Cancer in Humans

2.1 Introduction

A large number of case reports dating to the late 19th and early-to-mid-20th centuries raised suspicions that workers in various industries with exposure to chromium compounds, including chromate production, production of chromate pigments and chromium plating may be at risk of developing various cancers ([Newman, 1890](#); [Pfeil, 1935](#); [Teleky, 1936](#); [IARC, 1990](#)). Beginning in the mid-20th century, cohort studies were undertaken in these industries as well as in some other occupations and industries with potential exposure to chromium compounds, such as ferrochromium or stainless steel production, welding, leather tanning, and some others. By the 1980s considerable evidence had accumulated on cancer risks of chromium-exposed workers, and leading to the identification of chromium (VI) compounds as a human carcinogen ([IARC, 1990](#)).

The strongest evidence presented at the time concerned the lung. There was weaker and less consistent evidence of effects on gastrointestinal sites, mainly stomach, and some reports of excess risks at several other organs, such as pancreas, prostate and bladder. Furthermore, there were some case reports and small clusters of nasal or sinonasal cavity cancers in workers exposed

to chromium (VI). Based on the review of the previous *IARC Monograph*, and on a subsequent review of relevant epidemiological evidence accumulated since then, the Working Group focused the current review on those sites for which the evidence indicates possible associations with chromium (VI) compounds, namely: lung, nose, and nasal sinus. Because of recent controversy regarding possible effects on stomach cancer ([Proctor et al., 2002](#); [Beaumont et al., 2008](#)), the Working Group also reviewed relevant evidence for this organ. For other organs, the number of reports of excess risks is unremarkable in the context of the numbers of studies that have been conducted, and thus they have not been reviewed.

There have been at least 50 epidemiological studies that could be informative about cancer risks related to chromium (VI). Many of the studies have given rise to multiple reports; sometimes these simply represent follow-up updates, but often the different reports also present different types of analyses of subgroups or of case-control analyses within a cohort. Only a minority of the studies contain documented measurements of chromium (VI) exposure, particularly measurements that pertain to the era of exposure of the workforce that was investigated. It was therefore necessary to select and present the evidence according to the availability of relevant exposure information. The studies were triaged into the following categories:

1. Cohort studies in industries in which workers were highly likely to have been exposed at relatively high levels. This included workers in chromate production, chromate pigment production, and chromium electroplating.
2. Cohort studies in which workers were possibly exposed to relatively high levels but not with the same degree of certainty or concentration as those in category a. This included stainless steel welders.
3. Other studies in which workers may have been exposed to chromium (VI), but with lower likelihood or lower frequency or lower

concentrations than workers in categories 1) and 2). Among the occupations/industries in this category were ferrochromium and stainless steel production, mild steel welding, general paint production, general spray painting, tanneries, gold mining, and nickel plating.

Studies in category 3) were not routinely included in the current review because there were sufficiently informative studies in categories 1) and 2), except if the authors presented information indicative of exposure to non-negligible levels of chromium (VI).

Most of the informative evidence comes from industry-based cohort studies, some of which have been complemented by nested case-control analyses. One of the main limitations of industry-based cohort studies is the usual absence of information on smoking and other potential confounders aside from age, sex, and race. Nonetheless, except for some case-control studies of nasal cancer, the Working Group relied on cohort studies to provide informative results.

For each study selected, the Working Group chose the most recent publication; occasionally there were results in earlier papers that were also deemed important to present here. Further, in each publication there are typically a large number of results presented by organ site, by demographic characteristics of workers, by some index of duration or dose of exposure, and sometimes by analysing the data in a nested case-control fashion. For the purposes of the current review, the Working Group selected the key results from each publication, typically including the most general result available for workers exposed to chromium (VI) as well as a result for a subgroup characterized by relatively high duration or dose of exposure, when there were enough numbers in such a category.

2.2 Cancer of the lung

Almost all of the relative risk estimates for cancer of the lung presented in Table 2.1 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.1.pdf>) are greater than 1.0. Among chromate production workers, virtually all studies showed excess risks of lung cancer, except for a few estimates of risks for US workers hired since exposures were lowered ([Luippold et al., 2005](#)), but these latter analyses had few subjects and low power.

Similarly, studies of chromate pigment production workers tended to show elevated risks of lung cancer in nearly all the cohorts and subcohorts reported, though not every relative risk estimate was statistically significant. Also, among chromium electroplating workers, there was a clear pattern of excess risks in most cohorts. Workers in other industries who may have had somewhat lower levels of chromium (VI) exposure than those in the previously mentioned industries, had a less convincing set of relative risk estimates, though nearly all were above 1.0.

A few of the cohort studies collected high-quality smoking histories, and incorporated these into nested case-control analyses; these tended to show elevated risks independent of smoking. Several other studies had collected partial or representative smoking frequencies among their workers, and for most of these studies, the main results were unlikely to have been meaningfully confounded by smoking patterns in the workers.

A recent meta-analysis estimated an overall standardized mortality ratio (SMR) of 1.41 (95%CI: 1.35–1.47) for lung cancer among 47 studies of workers with possible chromium (VI) exposure ([Cole & Rodu, 2005](#)). [The Working Group noted that because of the great difficulty in establishing equivalencies between different studies in terms of the types and levels of exposures to chromium (VI), the summary estimates are difficult to interpret. Further, it appears

that some of the study populations in that meta-analysis overlapped with each other.]

In aggregate, the results continue to show that exposure to chromium (VI) increases the risks of lung cancer.

Very few of the epidemiological studies provided results relating to specific chromium (VI) compounds. Workers in chromate production were likely to have been exposed to mixtures of sodium, potassium, calcium and ammonium chromates and dichromates; the highest and most consistent excess risks were observed in these cohorts. Workers in chromate pigment production and spray painting were likely to have been exposed to zinc and/or lead chromates, also resulting in high risks. Steel smelting and welding probably resulted in exposure to alkaline chromates, and risks reported in these cohorts tended to be less clear than among the chromate producers and the chromate pigment producers. Because there seemed to be increased risks in diverse industries involving exposure to a variety of chromium (VI) compounds of varying solubilities, this observation argues for a general carcinogenic effect of chromium (VI).

2.3 Cancer of the nose and nasal sinus

Cancer of the nose and nasal sinus is extremely rare, the incidence of which is roughly 1/100th of the incidence of cancer of the lung ([Parkin et al., 1997](#)). In fact, most cohorts of workers exposed to chromium (VI) do not report on of the incidence of nose and nasal sinus cancers. [The Working Group noted that this could mean there were none in the cohort or that the investigators did not examine and report it.]

Table 2.2 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.2.pdf>) shows the nine (ten studies including [Sorahan et al., 1987](#)) cohort studies that did report how many nasal cancers occurred.

Combining those nine (ten) cohorts, there were mentions of 22 (25) cases of nasal or nasal sinus cancer. For the four cohorts that reported an expected as well as an observed number of cases, the aggregate was 12 observed and 1.5 expected giving an SMR of 8.0. Because several cohort studies failed to report any cases, it is difficult to integrate the appropriate observed and expected numbers from these studies into the overall estimate of risk from cohort studies. [The Working Group believed that many of the studies which made no report on nasal cancer actually had none.]

Case reports since the 1960s have reported 11 (12 including one case reported in [Enterline, 1974](#)) cases of nasal or nasal sinus cancer among chromate workers. Without any indication of person-years at risk, it is difficult to infer whether this represents an excess.

There have been three informative case-control studies on nasal and nasal sinus cancer. Two showed some indications of excess risk among workers with possible exposure to chromium (VI) compounds, but the study with the best exposure assessment protocol ([Luce et al., 1993](#)) reported no excess risks for workers exposed to chromium (VI).

In aggregate, the epidemiological evidence remains suggestive but inconclusive regarding the effect of chromium (VI) on nasal and nasal sinus cancers. [The Working Group noted that systematic confounding by nickel exposure is unlikely in the cohorts presented in Table 2.2 online.]

2.4 Cancer of the stomach

There is little evidence of an association between exposure to chromium (VI) and cancer of the stomach; there are as many point estimates above 1.0 as there are below. There has been concern about possible hazards related to the ingestion of chromium (VI) in drinking-water, and one study in the People's Republic of China

([Zhang & Li, 1987](#)) and a subsequent reanalysis of the Chinese data ([Beaumont et al., 2008](#)) seem to indicate a somewhat elevated risk of stomach cancer in which drinking-water was heavily polluted by a ferrochromium plant. However, one single ecological study does not constitute rigorous evidence of an association between exposure to chromium (VI) and cancer of the stomach.

See Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.3.pdf>.

2.5 Synthesis

The large majority of informative cohort studies indicate that there is an excess risk of lung cancer among workers exposed to chromium (VI), particularly in chromate production, chromate pigment production, and chromium electroplating. It is unlikely that any biases or chance can explain these findings.

There are some case reports, cohort studies and case-control studies that suggest a possible excess of cancer of the nose and nasal sinus among workers exposed to chromium (VI). However, this evidence is susceptible to publication and reporting biases because many of the cohort studies did not report on nasal cancers, and it is not clear how to evaluate the significance of the case reports.

There is little evidence that exposure to chromium (VI) causes stomach or other cancers.

3. Cancer in Experimental Animals

Chromium (VI) compounds have been tested for carcinogenicity by several routes in several animal species and strains ([IARC, 1990](#)), and the following paragraphs summarize some key findings from previous IARC evaluations of chromium (VI) compounds.

Calcium chromate induced lung tumours in mice (males and females combined) when given by inhalation ([Nettesheim et al., 1971](#)) and local tumours when given by intramuscular administration ([Payne, 1960](#)). In rats it caused lung tumours (adenoma, squamous cell carcinoma, or adenocarcinoma) when given by intratracheal administration ([Steinhoff et al., 1986](#)) or intrabronchial administration ([Levy & Venitt, 1986](#)), bronchial (carcinomas or squamous cell carcinomas) when administered by intrabronchial administration ([Levy et al., 1986](#)), and local tumours in rats treated by intrapleural ([Hueper, 1961](#); [Hueper & Payne, 1962](#)) or intramuscular administration ([Hueper & Payne, 1959, 1962](#); [Hueper, 1961](#); [Roe & Carter, 1969](#)).

Lead chromate (and its derived pigments), administered by subcutaneous injection ([Maltoni, 1974, 1976](#); [Maltoni et al., 1982](#)) or intramuscular injection cause malignant tumours at the site of injection and renal tumours ([Furst et al., 1976](#)) in rats. Subcutaneous administration of basic lead chromate caused local sarcomas in rats ([Maltoni, 1974, 1976](#); [Maltoni et al., 1982](#)). In rats, zinc chromates caused bronchial carcinomas when administered by intrabronchial implantation ([Levy et al., 1986](#)), and local tumours when given intrapleurally ([Hueper, 1961](#)), subcutaneously ([Maltoni et al., 1982](#)) or intramuscularly ([Hueper, 1961](#)). Strontium chromate also caused bronchial carcinomas (intrabronchial implantation administration) ([Levy et al., 1986](#)), and local sarcomas (intrapleural and intramuscular administration) in rats ([Hueper, 1961](#)).

Chromium trioxide when tested as a mist by inhalation caused nasal papillomas in mice ([Adachi & Takemoto, 1987](#)). Local tumours were observed in rats exposed to sintered chromium trioxide ([Hueper & Payne, 1959](#)). A low incidence of lung adenocarcinomas was induced after inhalation of chromium trioxide, and some lung tumours were observed in rats exposed by intrabronchial administration but neither were

statistically significant ([Adachi et al., 1986](#); [Levy et al., 1986](#); [Levy & Venitt, 1986](#)).

Sodium dichromate (when given by inhalation or intratracheal administration) caused lung tumours (benign and malignant) ([Glaser et al., 1986](#); [Steinhoff et al., 1986](#)) in rats.

3.1 Studies published since the previous *IARC Monograph*

Since the previous *IARC Monograph* ([IARC, 1990](#)), studies in experimental animals have been conducted to evaluate oral exposure to chromium (VI). [Table 3.1](#) summarizes the results of these studies, and the text below summarizes the major findings for each specific compound.

3.1.1 Sodium dichromate dihydrate

The National Toxicology Program (NTP) conducted 2-year drinking-water studies of sodium dichromate dihydrate in male and female B6C3F₁ mice, and in male and female F344 rats. In rats, sodium dichromate dihydrate significantly increased the incidence of squamous cell epithelium tumours of the oral mucosa or tongue in the high-dose groups (516 mg/L) of males and females. Trend analysis indicated a dose-response relationship in both males and females. In mice, sodium dichromate dihydrate significantly increased tumours (adenomas or carcinomas) of the small intestine (duodenum, jejunum, or ileum) in the two-highest dose groups of males (85.7 and 257.4 mg/L) and females (172 and 516 mg/L). Dose-response relationships were observed in both sexes ([NTP, 2008](#)).

3.1.2 Potassium chromate

[Davidson et al. \(2004\)](#) studied the effects of potassium chromate on ultraviolet(UV)-induced skin tumours in female hairless mice (CRL: SK1-hrBR). Mice were exposed to UV alone,

various concentration of potassium chromate alone (given in the drinking-water), and UV together with various concentrations of potassium chromate. Administration of drinking-water containing potassium chromate did not induce skin tumours alone. However, chromate treatment significantly increased the multiplicity of UV-induced skin tumours, and the multiplicity of malignant UV-induced skin tumours. Similar results were found in male and female hairless mice ([Uddin et al., 2007](#)). The analysis of skin indicated that UV treatment increased the level of chromium in the exposed skin ([Davidson et al., 2004](#)).

3.2 Synthesis

The administration of calcium chromate in mice and sodium dichromate in rats by inhalation caused lung cancer. Calcium chromate and sodium dichromate administered by intratracheal instillation caused lung cancer in rats. Intratracheal administration of calcium chromate, zinc chromate, and strontium chromate caused lung cancer in rats. Several chromium compounds by repository injection (calcium chromate, lead chromate, zinc chromate, strontium chromate) caused local sarcomas. Oral administration of sodium dichromate to rats and mice caused cancer of the oral cavity and of the gastrointestinal tract. Potassium chromate given orally, although not given alone, enhanced UV-induced skin carcinogenesis, indicating tumour systemic effects.

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Table 3.1 Studies of cancer in experimental animals exposed to chromium (VI) (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance ^a	Comments
Sodium dichromate dihydrate				
Rat, F344/N (M, F) 2 yr NTP (2008)	Drinking-water 0, 14.3, 57.3 172, 516 mg/L Average daily doses: M-0, 0.6, 2.2 6, 17 mg/kg bw F-0, 0.7, 2.7, 7, 20 mg/kg bw <i>ad libitum</i> 50/group/sex	Oral mucosa (squamous cell carcinomas): ^b M-0/50, 0/50, 0/49, 0/50, 6/49 (12%) F-0/50, 0/50, 0/50, 2/50 (4%), 11/50 (22%) Tongue (squamous cell papillomas or carcinomas): M-0, 1, 0, 0, 1 F-1, 1, 0, 1, 0 Oral mucosa or tongue: ^c M-0/50, 1/50 (2%), 0/49, 0/50, 7/49 (14%) F-1/50 (2%), 1/50 (2%), 0/50, 2/50 (4%), 11/50 (22%)	M: $P < 0.05$ (high dose); $P_{\text{trend}} < 0.001$ F: $P < 0.001$ (high dose); $P_{\text{trend}} < 0.001$ M: $P < 0.01$; $P_{\text{trend}} < 0.001$ F: $P < 0.01$ (high dose); $P_{\text{trend}} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased bw in high-dose males and females Decreased water consumption of the 2 highest doses
Mouse, B6C3F ₁ (M, F) 2 yr NTP (2008)	Drinking-water M: 0, 14.3, 28.6, 85.7, 257.4 mg/L F: 0, 14.3, 57.3, 172, 516 mg/L Average daily doses: M-0, 1.1, 2.6, 7, 17 mg/kg bw F-0, 1.1, 39.9, 9, 25 mg/kg bw <i>ad libitum</i> 50/group/sex	Small intestine (adenomas): M-1/50 (2%), 1/50 (2%), 1/50 (2%), 5/50 (10%), 17/50 (34%) F-0/50, 1/50 (2%), 2/50 (4%), 15/50 (30%), 16/50 (32%) Small intestine (carcinomas): M-0/50, 2/50 (4%), 1/50 (2%), 3/50 (6%), 5/50 (10%) F-1/50 (2%), 0/50, 2/50 (4%), 3/50 (6%), 7/50 (14%) Small intestine (adenomas or carcinomas): ^d M-1/50 (2%), 3/50 (6%), 2/50 (4%), 7/50 (14%), 20/50 (40%) F-1/50 (2%), 1/50 (2%), 4/50 (8%), 17/50 (34%), 22/50 (44%)	M: $P < 0.001$ (high dose); $P_{\text{trend}} < 0.001$ F: $P < 0.001$ (2 highest doses); $P_{\text{trend}} < 0.001$ M: $P < 0.05$ (high dose); $P_{\text{trend}} < 0.05$ F: $P < 0.05$ (high dose); $P_{\text{trend}} < 0.001$ M: $P < 0.001$ (high dose), $P < 0.05$ (85.7 mg/L), $P_{\text{trend}} < 0.001$ F: $P < 0.001$ (2 highest doses 172 and 516 mg); $P_{\text{trend}} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased body weight in 2 highest female dose groups Decreased water consumption of the 2 highest doses (males and females) Most of the tumours were located in the duodenum

Chromium (VI) compounds

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance ^a	Comments
Potassium chromate (K_2CrO_4)				
Mouse, CRL: Sk1- hrBR (F) 224 d Davidson et al. (2004)	Group 1: Controls Group 2: UV only Group 3: 2.5 ppm K_2CrO_4 Group 4: 5 ppm K_2CrO_4 Group 5: UV + 0.5 ppm K_2CrO_4 Group 6: UV + 2.5 ppm K_2CrO_4 Group 7: UV + 5 ppm K_2CrO_4 UV: 1 mo after K_2CrO_4 1.1 kJ/m ² 3 d/wk for 3 mo, followed by 1 wk break, and 1.3 kJ/m ² , 2 d/wk for 3 mo K_2CrO_4 : 182 d, added to drinking- water every 7–10 d 120 animals	Skin (tumours): Groups 1, 3, 4—no tumours Number of tumours (> 2mm/no of mice at 182 d): Group 2–12/15 (0.8) Group 5–16/12 (1.39) Group 6–50/19 (2.63) Group 7–94/19 (5.02)	Group 6 vs Group 2, $P < 0.05$ Group 7 vs Group 2, $P < 0.01$	Age at start, 6 wk Chromium-only treatment had no effects on bw or toxicity Levels of chromium were measured in dorsal thoracic skin and abdominal skin in Groups 1, 4, and 7 UV + chromium had significantly higher chromium levels in back and underbelly skin

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Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance ^a	Comments
Mouse, CRL: Sk1- hrBR (M, F) 224 d Uddin et al. (2007)	Groups: treatment, <i>n</i> Group 1a: UV, 10 Group 1a: UV + 2.5 ppm K ₂ CrO ₄ , 10 Group 1c: UV + 5 ppm K ₂ CrO ₄ , 10 Group 2a: UV + 5 ppm K ₂ CrO ₄ , 10 Group 2b: UV + 5 ppm K ₂ CrO ₄ + Vitamin E, 10 Group 2c: UV + 5 ppm K ₂ CrO ₄ + selenium, 10 Mice administered K ₂ CrO ₄ in drinking-water at 3 wk of age. 3 wk later UV treatment (1.0 kJ/m ²) 3 d/wk for 26 wk Vitamin E: 62.5 IU/kg Selenium: 5 mg/kg Group 1–males, Group 2–females (30/group)	Skin (number of tumours/mice at 26 wk): M– Group 1a: 1.9 ± 0.4 Group 1b: 5.9 ± 0.8 Group 1c: 8.6 ± 0.9 F– Group 2a: 3.9 ± 0.6 Group 2b: 3.5 ± 0.6 Group 2c: 3.6 ± 0.6	Group 1b vs 1a, <i>P</i> < 0.001 Group 1c vs 1a, <i>P</i> < 0.0001	Age, 3 wk Chromium had no effect on growth of the mice. Chromium levels in skin increased with dose Chromium also decreased the time until appearance of first tumours in males

^a *P*-values for calculated by Poly 3- for NTP studies, which accounts for differential mortality in animals that do not reach terminal sacrifice.

^b Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 0/300, F: 0/300.

^c Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 2/300, range 0 to 2%; F: 3/300, range 0 to 2%.

^d Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M:11/299, range 0–10%; F: 4/350, range 0 to 4%.

^e [Borneff et al. \(1968\)](#) published in German.

^f No information on tumour incidence of this group was reported by [Sedman et al. \(2006\)](#).

^g Two-Tailed Fisher Exact Test; Authors stated significant but did not provide *P*-value.

^h Untreated and chromium only, controls not included since no tumours were observed in the study by [Davidson et al. \(2004\)](#).

bw, body weight; d, day or days; F, female; M, male; mo, month or months; UV, ultraviolet; vs, versus; wk, week or weeks; yr, year or years

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In humans, the absorption, retention, and elimination of chromium compounds after exposure by inhalation depend on the solubility and particle size of the particular compound inhaled (for an extensive review, see [ATSDR, 2008b](#)). The retention may range from several hours to weeks. Inhaled chromium (VI) is readily absorbed from the respiratory tract. The degree of absorption depends on the physical and chemical properties of the particles (size, solubility), and the extent of reduction of the hexavalent form to chromium (III), which is absorbed to a much lesser extent. Thus, after intratracheal instillation in rats, 53–85% of chromium (VI) compounds with a particle size < 5 µm are absorbed into the bloodstream, with higher absorption rates in case of more soluble compounds; the rest remains in the lungs. For comparison, absorption of chromium (III) from the respiratory tract is only 5–30% ([ATSDR, 2008b](#)). The same factors mentioned above apply to absorption from the gastrointestinal tract, although absorption by this route is generally much less compared with that in the respiratory tract. Average absorption fractions determined in human volunteers for chromium (III) or chromium (VI) were reported as 0.13% or 6.9%, respectively. Chromium (VI) can penetrate human skin to some extent ([ATSDR, 2008b](#)).

In humans and rodents, absorbed chromium (VI) is distributed in nearly all tissues, with the highest concentrations found in the kidney, liver, and bone. Studies conducted by the NTP in male rats and female mice orally exposed to chromium (VI) for 2 years showed dose-related and time-dependent increases in total chromium concentrations in red cells, plasma, and in several organs. The total chromium content of the red cells was higher than that of plasma. The

concentration of total chromium in the forestomach was found to be markedly higher in mice than in rats ([NTP, 2008](#)).

Within the human body, chromium (VI) undergoes a series of reduction steps to form the thermodynamically stable chromium (III). When reduction occurs extracellularly, this process can be considered as detoxification because the cell membrane is a nearly impermeable barrier for chromium (III). The remaining chromium (VI) is present as a mixture of chromate (CrO_4^{2-}) and hydrochromate (HCrO_4^-); because water-soluble chromates are iso-structural with sulfate and phosphate ions, they are readily taken up by sulfate channels. In case of poorly water-soluble chromates, particles of < 5 µm can be phagocytosed, and gradually dissolved intracellularly. Within the cell, chromium (VI) is reduced stepwise to chromium (III), giving rise to reactive intermediates as well as DNA and protein adducts. In blood, chromium (VI) is taken up into red blood cells, is reduced, and then bound to proteins. After exposure by inhalation, excretion occurs predominantly via the urine. Due to the low absorption of chromium compounds from the gastrointestinal tract, the major pathway of elimination after oral exposure is through the faeces ([ATSDR, 2008b](#)).

4.2 Genetic and related effects

The oxidation state of chromium is the most important factor when considering its biochemical activity ([Beyersmann & Hartwig, 2008](#); [Salnikow & Zhitkovich, 2008](#)). Chromium (VI), but not chromium (III) compounds, have been shown to exert genotoxicity both *in vivo* and *in vitro*.

Lymphocytes of workers exposed to dusts of chromium (VI) compounds showed elevated frequencies of DNA strand breaks ([Gambelunghe et al., 2003](#)), sister chromatid exchange ([Wu et al., 2001](#)), and micronuclei ([Vaglenov et al., 1999](#); [Benova et al., 2002](#)).

After intratracheal instillation in rats, chromium (VI) induced DNA strand breaks in lymphocytes ([Gao et al., 1992](#)). After intraperitoneal injection of chromium (VI) to mice, micronuclei were induced in bone marrow. In contrast, no micronucleus induction was observed after oral administration, indicating that chromium (VI) does not reach the target cells to a high extent by this route of exposure ([De Flora et al., 2006](#)). Chromium (VI) induces dominant lethal mutations in male mice ([Paschin et al., 1982](#)).

In vitro, soluble chromium (VI) compounds are mutagenic in mammalian and bacterial test systems ([De Flora et al., 1990](#)).

4.2.1 DNA damage

Chromium (VI) is unreactive towards DNA under physiological conditions. According to the uptake–reduction model originally established by [Wetterhahn et al. \(1989\)](#), chromium (VI) undergoes a series of reduction steps in cells, to form the thermodynamically stable chromium (III). Intracellular reduction does not require enzymatic steps but is mediated by direct electron transfer from ascorbate and non-protein thiols, such as glutathione and cysteine. During the reduction process, variable amounts of chromium (V) and chromium (IV) as well as organic radical species are generated; their exact nature, however, depends largely on the reducing species ([Wetterhahn & Hamilton, 1989](#)). Furthermore, comparative *in-vivo* and *in-vitro* studies revealed a major impact of the intracellular reductants on the nature and biological consequences of the resultant DNA lesions.

The major intracellular reductant under physiological conditions appears to be ascorbate, reaching millimolar concentrations in human tissues, and accounting for about 90% of chromium (VI) reduction reactions *in vivo* ([Standeven et al., 1992](#)). In contrast, only micromolar concentrations of ascorbate are usually present in cell cultures ([Quievryn et al., 2002](#)), which leads to

an increase in thiol-mediated chromate reduction. When ascorbate is the reductant, two electrons are transferred, and chromium (IV) but not chromium (V) is generated as the first intermediate, whereas with cysteine as a reductant, predominantly chromium (V) is formed due to one-electron transfers ([Stearns & Wetterhahn, 1994](#)). In both cases, the final product is chromium (III), which reacts to produce different types of DNA lesions.

DNA lesions generated after exposure to chromium (VI) include chromium (III)–DNA adducts, DNA–protein and DNA–DNA interstrand crosslinks, DNA breaks as well as several oxidative DNA–base modifications. The predominant form of chromium (III)–DNA adducts are ternary adducts, where chromium forms a link between DNA and small molecules such as cysteine, histidine, glutathione or ascorbate, presumably arising from preformed chromium–ligand complexes during the reduction process. These adducts are formed primarily at phosphate groups, but the subsequent partial formation of chelates involving the phosphate group and the *N*⁷-position of guanine have been suggested. Chelates formed from chromium–ascorbate particularly are potent premutagenic DNA lesions ([Zhirkovich et al., 2001](#)).

The formation of DNA–protein crosslinks after chromate exposure is well established, but is estimated to account for less than 1% of chromium–DNA adducts. Biological consequences are likely to be disturbances of DNA replication and transcription. The formation of DNA–DNA crosslinks appears to be restricted to certain *in-vitro* conditions, due to severe steric hindrance upon intercalation of octahedral chromium (III) complexes ([Zhirkovich, 2005](#)).

DNA single-strand breaks may arise due to the reaction of chromium (V) with hydrogen peroxide, forming hydroxyl radicals. Nevertheless, if ascorbate is the predominant reductant under *in-vivo* conditions, the generation of chromium (V) and thus, single-strand

breaks, appears to be of minor importance ([Quievryn et al., 2003](#)). Cytogenetic alterations in chromium (VI)-exposed cells in culture and *in vivo*, such as increased frequencies of chromosomal breaks and micronuclei, are suggested to be due to DNA double-strand breaks, produced by a cell-replication-dependent mechanism in the G2 phase of the cell cycle. Recent evidence suggests the involvement of mismatch repair in the formation of double-strand breaks. Thus, highly mutagenic ascorbate–chromium–DNA adducts lead to the error-prone repair of double-strand breaks through non-homologous end-joining. Furthermore, they induce mismatches during replication, leading to aberrant mismatch repair. Based on these findings, a model has been created to show that chronic exposure to toxic doses of chromium (VI) provokes the selective outgrowth of mismatch-repair-deficient clones with high rates of spontaneous mutagenesis, and thus, genomic instability ([Reynolds et al., 2007](#); [Salnikow & Zhitkovich, 2008](#)). In support of this model, chromium-induced cancers in exposed workers were associated with microsatellite instability and exhibited the loss of expression of MLH1, which is one of the essential mismatch-repair proteins ([Takahashi et al., 2005](#)).

4.2.2 Oxidative stress

In the reduction of chromium (VI) to chromium (III) by cellular reductants, potentially toxic intermediates (oxygen radicals, sulfur radicals, and chromium radicals) are generated ([Yao et al., 2008](#)). In a cell-free system, chromium (VI) reacted with glutathione to form chromium (V) and thiyl radicals ([Wetterhahn et al., 1989](#)). Furthermore, after reduction of chromium (VI) by glutathione, chromium (V) can undergo Fenton-type reactions, producing hydroxyl radicals ([Shi et al., 1994](#)), and 8-oxoguanine in isolated DNA ([Faux et al., 1992](#)). In cultured mammalian cells, chromium (VI) induced the formation of superoxide and nitric oxide

([Hassoun & Stohs, 1995](#)). The administration of chromium (VI) to animals, which have higher tissue levels of ascorbate compared with cultured cells, did not induce the formation of 8-oxoguanine ([Yuann et al., 1999](#)). This may be due to the lack of chromium (V) formation when ascorbate is the predominant reducing agent.

4.2.3 Further potentially relevant mechanisms

Besides direct genotoxic effects of chromium (VI) metabolites, chromate may activate various mitogen-activated protein kinases as well as transcription factors involved in inflammation and tumour growth. Nevertheless, because these effects have been observed in cell-culture systems and no distinct effects of chromium (VI) on cell proliferation have been shown, the relevance of these observations remains unclear at present. Perhaps of higher impact are the aneugenic properties of chromium (VI). Chronic treatment with lead-chromate particles induced neoplastic transformation of human bronchial cells, which was accompanied by centrosome amplification, and an increase in aneuploid metaphases ([Xie et al., 2007](#)).

4.3 Synthesis

Several mechanisms are involved in the carcinogenesis induced by chromium (VI) that include the induction of DNA damage, the generation of oxidative stress and aneuploidy, leading to cell transformation. With respect to DNA damage, the spectrum of induced lesions appears to depend strongly on the cellular reductant involved. Thus, under physiological conditions with ascorbate as the major reductant, the generation of premutagenic ternary chromium–ascorbate–DNA adducts appears to be of major relevance, which may be linked to the increased number of mismatch-repair-resistant cells observed in chromate-induced lung tumours.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of chromium (VI) compounds. Chromium (VI) compounds cause cancer of the lung. Also positive associations have been observed between exposure to Chromium (VI) compounds and cancer of the nose and nasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of chromium (VI) compounds.

Chromium (VI) compounds are *carcinogenic to humans* (Group 1).

References

- Adachi S & Takemoto K (1987). Occupational lung cancer. A comparison between humans and experimental animals *Sangyo Igaku*, 29: 345–357. PMID:2831418
- Adachi S, Yoshimura H, Katayama H, Takemoto K (1986). Effects of chromium compounds on the respiratory system. Part 4. Long-term inhalation of chromic acid mist in electroplating to ICR female mice *Sangyo Igaku*, 28: 283–287. PMID:3784105
- ATSDR (2000). *Chromium (TP-7)* In: *Toxicological Profile*. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, pp. 461.
- ATSDR (2008a). *Chromium (TP-7)* In: *Toxicological Profile*. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, pp. 610.
- ATSDR (2008b) *Toxicological Profile for Chromium*. Available at: <http://www.atsdr.cdc.gov/toxprofiles/tp7.html#bookmark09>
- Beaumont JJ, Sedman RM, Reynolds SD *et al.* (2008). Cancer mortality in a Chinese population exposed to hexavalent chromium in drinking water. *Epidemiology*, 19: 12–23. doi:10.1097/EDE.0b013e31815cea4c PMID:18091413
- Benova D, Hadjidekova V, Hristova R *et al.* (2002). Cytogenetic effects of hexavalent chromium in Bulgarian chromium platers. *Mutat Res*, 514: 29–38. PMID:11815242
- Beyersmann D & Hartwig A (2008). Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol*, 82: 493–512. doi:10.1007/s00204-008-0313-y PMID:18496671
- Blade LM, Yencken MS, Wallace ME *et al.* (2007). Hexavalent chromium exposures and exposure-control technologies in American enterprise: results of a NIOSH field research study. *J Occup Environ Hyg*, 4: 596–618. doi:10.1080/15459620701463183 PMID:17577750
- Borneff J, Engelhardt K, Griem W *et al.* (1968). Carcinogens in water and soil. XXII. Experiment with 3,4-benzopyrene and potassium chromate in mice drink *Arch Hyg Bakteriol*, 152: 45–53. PMID:5707368
- CAREX Canada (2011). Available at: http://www.carexcanada.ca/en/chromium_%28hexavalent%29/occupational_exposure_estimates/phase_2/
- Cole P & Rodu B (2005). Epidemiologic studies of chrome and cancer mortality: a series of meta-analyses. *Regul Toxicol Pharmacol*, 43: 225–231. doi:10.1016/j.yrtph.2005.06.009 PMID:16099572
- Davidson T, Kluz T, Burns F *et al.* (2004). Exposure to chromium (VI) in the drinking water increases susceptibility to UV-induced skin tumors in hairless mice. *Toxicol Appl Pharmacol*, 196: 431–437. doi:10.1016/j.taap.2004.01.006 PMID:15094314
- De Flora S, Bagnasco M, Serra D, Zancacchi P (1990). Genotoxicity of chromium compounds. A review. *Mutat Res*, 238: 99–172. PMID:2407950
- De Flora S, Iltcheva M, Balansky RM (2006). Oral chromium(VI) does not affect the frequency of micronuclei in hematopoietic cells of adult mice and of transplacentally exposed fetuses. *Mutat Res*, 610: 38–47. PMID:16872865
- Ellis AS, Johnson TM, Bullen TD (2002). Chromium isotopes and the fate of hexavalent chromium in the environment. *Science*, 295: 2060–2062. doi:10.1126/science.1068368 PMID:11896274
- Enterline PE (1974). Respiratory cancer among chromate workers. *J Occup Med*, 16: 523–526. PMID:4843401
- EVM Expert Group on Vitamins and Minerals Secretariat (2002). *Review of chromium*. UK: EVM/99/26. REVISED AUG 2002, 25. 2002.
- Faux SP, Gao M, Chipman JK, Levy LS (1992). Production of 8-hydroxydeoxyguanosine in isolated DNA by chromium(VI) and chromium(V). *Carcinogenesis*, 13: 1667–1669. doi:10.1093/carcin/13.9.1667 PMID:1327573
- Furst A, Schlauder M, Sasmore DP (1976). Tumorigenic activity of lead chromate. *Cancer Res*, 36: 1779–1783. PMID:1268834
- Gambelungha A, Piccinini R, Ambrogi M *et al.* (2003). Primary DNA damage in chrome-plating workers. *Toxicology*, 188: 187–195. PMID:12767690
- Gao M, Binks SP, Chipman JK *et al.* (1992). Induction of DNA strand breaks in peripherally lymphocytes by soluble chromium compounds. *Hum Exp Toxicol*, 11: 77–82. doi:10.1177/096032719201100203 PMID:1349223
- Gianello G, Masci O, Carelli G *et al.* (1998). Occupational exposure to chromium – an assessment of environmental pollution levels and biological monitoring of

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- exposed workers. *Ind Health*, 36: 74–77. doi:10.2486/indhealth.36.74 PMID:9473863
- Glaser U, Hochrainer D, Klöppel H, Oldiges H (1986). Carcinogenicity of sodium dichromate and chromium (VI/III) oxide aerosols inhaled by male Wistar rats. *Toxicology*, 42: 219–232. doi:10.1016/0300-483X(86)90011-9 PMID:3798470
- Guertin J, Jacobs JA, Avakian CP (2004). *Chromium (VI) Handbook*. Boca Raton, FL: CRC Press, pp. 800.
- Hall R, Rhodes D, Page E (2005). *Evaluation of worker exposures during the manufacturing of high quality corrosive resistant stainless steel products and fabricated piping systems*. American Industrial Hygiene Conference and Expo, Anaheim, CA: May 21–26, 2005. Fairfax, VA: American Industrial Hygiene Association, pp. 59.
- Hassoun EA & Stohs SJ (1995). Chromium-induced production of reactive oxygen species, DNA single-strand breaks, nitric oxide production, and lactate dehydrogenase leakage in J774A.1 cell cultures. *J Biochem Toxicol*, 10: 315–321. doi:10.1002/jbt.2570100606 PMID:8934634
- Hueper WC (1961). Environmental carcinogenesis and cancers. *Cancer Res*, 21: 842–857. PMID:13716558
- Hueper WC & Payne WW (1959). Experimental cancers in rats produced by chromium compounds and their significance to industry and public health. *Am Ind Hyg Assoc J*, 20: 274–280. PMID:13670103
- Hueper WC & Payne WW (1962). Experimental studies in metal carcinogenesis. Chromium, nickel, iron, arsenic. *Arch Environ Health*, 5: 445–462. PMID:13955488
- IARC (1973). Some inorganic and organometallic compounds. *IARC Monogr Eval Carcinog Risk Chem Man*, 2: 1–181.
- IARC (1979). Chemicals and industrial processes associated with cancer in humans. IARC Monographs, volumes 1 to 20. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 1: 1–71. PMID:296141
- IARC (1980). Some metals and metallic compounds. *IARC Monogr Eval Carcinog Risk Chem Hum*, 23: 1–415. PMID:6933135
- IARC (1982). Chemicals, industrial processes and industries associated with cancer in humans (IARC Monographs, volumes 1 to 29). *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 4: 1–292.
- IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203
- IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49: 1–648. PMID:2232124
- Kotaš J & Stasicka Z (2000). Chromium occurrence in the environment and methods of its speciation. *Environ Pollut*, 107: 263–283. doi:10.1016/S0269-7491(99)00168-2 PMID:15092973
- Krystek P & Ritsema R (2007). Monitoring of chromium species and 11 selected metals in emission and immersion of airborne environment. *Int J Mass Spectrom*, 265: 23–29. doi:10.1016/j.ijms.2007.05.003
- Levy LS, Martin PA, Bidstrup PL (1986). Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. *Br J Ind Med*, 43: 243–256. PMID:3964573
- Levy LS & Venitt S (1986). Carcinogenicity and mutagenicity of chromium compounds: the association between bronchial metaplasia and neoplasia. *Carcinogenesis*, 7: 831–835. doi:10.1093/carcin/7.5.831 PMID:3698209
- Lide DR, editor (2008). *CRC Handbook of Chemistry and Physics*, 88th ed. New York, NY: CRC Press, Taylor & Francis Group, pp. 4–50.
- Luce D, Gérin M, Leclerc A *et al.* (1993). Sinonasal cancer and occupational exposure to formaldehyde and other substances. *Int J Cancer*, 53: 224–231. doi:10.1002/ijc.2910530209 PMID:8425759
- Luippold RS, Mundt KA, Dell LD, Birk T (2005). Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. *J Occup Environ Med*, 47: 381–385. doi:10.1097/01.jom.0000158703.32263.0d PMID:15824629
- Lurie P & Wolfe SM (2002). Continuing exposure to hexavalent chromium, a known lung carcinogen: an analysis of OSHA compliance inspections, 1990–2000. *Am J Ind Med*, 42: 378–383. doi:10.1002/ajim.10128 PMID:12382250
- Maltoni C (1974). Occupational carcinogenesis. *Excerpta med int Congr Ser*, 322: 19C.bib_lpa\$-Char>26C.bib_lpa\$-Char.
- Maltoni C (1976). Occupational carcinogenesis. Predictive value of carcinogenesis bioassays. *Ann NY Acad Sci*, 271: 1 Neoplasia in431–443. doi:10.1111/j.1749-6632.1976.tb23144.x PMID:1069535
- Maltoni C, Morisi L, Chieco P (1982). Experimental approach to the assessment of the carcinogenic risk of industrial inorganic pigments *Adv mod environ Toxicol*, 2: 7792.
- Mukherjee AB (1998). Chromium in the environment of Finland. *Sci Total Environ*, 217: 9–19. doi:10.1016/S0048-9697(98)00163-6 PMID:9695169
- Nettesheim P, Hanna MG Jr, Doherty DG *et al.* (1971). Effect of calcium chromate dust, influenza virus, and 100 R whole-body x radiation on lung tumor incidence in mice. *J Natl Cancer Inst*, 47: 1129–1144. PMID:10787327
- Newman D (1890). A case of adeno-carcinoma of the left inferior turbinated body, and perforation of the nasal septum, in the person of a worker in chrome pigments. *Glasg Med J*, 33: 469–470.
- NTP (2005). NTP 11th Report on Carcinogens *Rep Carcinog*, 11: 1–A32. PMID:19826456

IARC MONOGRAPHS – 100C

- NTP (2008). NTP Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate (CAS No. 7789-12-0) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). *Natl Toxicol Program Tech Rep Ser*, 546: 1-192. PMID:18716633
- OHCOV (2005). *Hexavalent Chromium*. Ontario, Canada: Occupational Health Clinics for Ontario Workers Inc.
- OSHA; Occupational Safety and Health Administration. Department of Labor (2006). Occupational exposure to hexavalent chromium. Final rule. *Fed Regist*, 71: 10099-10385. PMID:16528853
- Parkin D, Whelan S, Ferlay J *et al.*, editors (1997). *Cancer Incidence in Five Continents. volume VII*. Lyon: IARC Press.
- Paschin YV, Zacepilova TA, Kozachenko VI (1982). Induction of dominant lethal mutations in male mice by potassium dichromate. *Mutat Res*, 103: 345-347. doi:10.1016/0165-7992(82)90065-3 PMID:7087995
- Paustenbach DJ, Finley BL, Mowat FS, Kerger BD (2003). Human health risk and exposure assessment of chromium (VI) in tap water. *J Toxicol Environ Health, Part A*, 66: 1295-1339. doi:10.1080/15287390306388 PMID:12851114
- Payne WW (1960). Production of cancers in mice and rats by chromium compounds. *AMA Arch Ind Health*, 21: 530-535. PMID:14431169
- Pfeil E (1935). Lung tumors as occupational disease in chromate plants (Ger.). *Dtsch Med Wochenschr*, 61: 1197-1200. doi:10.1055/s-0028-1122461
- Proctor DM, Otani JM, Finley BL *et al.* (2002). Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. *J Toxicol Environ Health A*, 65: 701-746. doi:10.1080/00984100290071018 PMID:12028825
- Proctor DM, Panko JP, Liebig EW *et al.* (2003). Workplace airborne hexavalent chromium concentrations for the Painesville, Ohio, chromate production plant (1943-1971). *Appl Occup Environ Hyg*, 18: 430-449. doi:10.1080/10473220301421 PMID:12746066
- Quievryn G, Messer J, Zhitkovich A (2002). Carcinogenic chromium(VI) induces cross-linking of vitamin C to DNA in vitro and in human lung A549 cells. *Biochemistry*, 41: 3156-3167. doi:10.1021/bi011942z PMID:11863455
- Quievryn G, Peterson E, Messer J, Zhitkovich A (2003). Genotoxicity and mutagenicity of chromium(VI)/ascorbate-generated DNA adducts in human and bacterial cells. *Biochemistry*, 42: 1062-1070. doi:10.1021/bi0271547 PMID:12549927
- Reinds GJ, Groenenberg JE, de Vries W (2006). *Critical loads of copper, nickel zinc, arsenic, chromium and selenium for terrestrial ecosystems at a European scale: A preliminary assessment (Alterra Report 1355)*. Wageningen, pp. 45.
- Reynolds M, Stoddard L, Bespalov I, Zhitkovich A (2007). Ascorbate acts as a highly potent inducer of chromate mutagenesis and clastogenesis: linkage to DNA breaks in G2 phase by mismatch repair. *Nucleic Acids Res*, 35: 465-476. doi:10.1093/nar/gkl1069 PMID:17169990
- Roe FJ & Carter RL (1969). Chromium carcinogenesis: calcium chromate as a potent carcinogen for the subcutaneous tissues of the rat. *Br J Cancer*, 23: 172-176. PMID:5768433
- Rowbotham AL, Levy LS, Shuker LK (2000). Chromium in the environment: an evaluation of exposure of the UK general population and possible adverse health effects. *J Toxicol Environ Health B Crit Rev*, 3: 145-178. doi:10.1080/10937400050045255 PMID:10911983
- Salnikow K & Zhitkovich A (2008). Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. *Chem Res Toxicol*, 21: 28-44. doi:10.1021/tx700198a PMID:17970581
- Sedman RM, Beaumont J, McDonald TA *et al.* (2006). Review of the evidence regarding the carcinogenicity of hexavalent chromium in drinking water. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*, 24: 155-182. PMID:16690539
- Shi X, Mao Y, Knapton AD *et al.* (1994). Reaction of Cr(VI) with ascorbate and hydrogen peroxide generates hydroxyl radicals and causes DNA damage: role of a Cr(IV)-mediated Fenton-like reaction. *Carcinogenesis*, 15: 2475-2478. doi:10.1093/carcin/15.11.2475 PMID:7955094
- Sorahan T, Burges DC, Waterhouse JA (1987). A mortality study of nickel/chromium platers. *Br J Ind Med*, 44: 250-258. PMID:3567099
- Standeven AM, Wetterhahn KE, Kato R (1992). Ascorbate is the principal reductant of chromium(VI) in rat lung ultrafiltrates and cytosols, and mediates chromium-DNA binding in vitro. *Carcinogenesis*, 13: 1319-1324. doi:10.1093/carcin/13.8.1319 PMID:1499083
- Stearns DM & Wetterhahn KE (1994). Reaction of chromium(VI) with ascorbate produces chromium(V), chromium(IV), and carbon-based radicals. *Chem Res Toxicol*, 7: 219-230. doi:10.1021/tx00038a016 PMID:8199312
- Steinhoff D, Gad SC, Hatfield GK, Mohr U (1986). Carcinogenicity study with sodium dichromate in rats. *Exp Pathol*, 30: 129-141. PMID:3792485
- Takahashi Y, Kondo K, Hirose T *et al.* (2005). Microsatellite instability and protein expression of the DNA mismatch repair gene, hMLH1, of lung cancer in chromate-exposed workers. *Mol Carcinog*, 42: 150-158. doi:10.1002/mc.20073 PMID:15605365
- Teleky L (1936). Cancer in chromium workers (Ger.). *Dtsch Med Wochenschr*, 62: 1353 doi:10.1055/s-0028-1141271
- Teschke K, Ahrens W, Andersen A *et al.* (1999). Occupational exposure to chemical and biological agents in the nonproduction departments of pulp, paper, and paper product mills: an international study. *Am Ind Hyg Assoc J*, 60: 73-83. PMID:10028618
- Uddin AN, Burns FJ, Rossman TG *et al.* (2007). Dietary chromium and nickel enhance UV-carcinogenesis

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- in skin of hairless mice. *Toxicol Appl Pharmacol*, 221: 329–338. doi:10.1016/j.taap.2007.03.030 PMID:17499830
- Vaglenov A, Nosko M, Georgieva R *et al.* (1999). Genotoxicity and radioresistance in electroplating workers exposed to chromium. *Mutat Res*, 446: 23–34. PMID:10613183
- Wetterhahn KE & Hamilton JW (1989). Molecular basis of hexavalent chromium carcinogenicity: effect on gene expression. *Sci Total Environ*, 86: 113–129. doi:10.1016/0048-9697(89)90199-X PMID:2602931
- Wetterhahn KE, Hamilton JW, Aiyar J *et al.* (1989). Mechanism of chromium(VI) carcinogenesis. Reactive intermediates and effect on gene expression. *Biol Trace Elem Res*, 21: 405–411. doi:10.1007/BF02917282 PMID:2484620
- Wu FY, Wu WY, Kuo HW *et al.* (2001). Effect of genotoxic exposure to chromium among electroplating workers in Taiwan. *Sci Total Environ*, 279: 21–28. doi:10.1016/S0048-9697(01)00685-4 PMID:11712598
- Xie H, Holmes AL, Wise SS *et al.* (2007). Neoplastic transformation of human bronchial cells by lead chromate particles. *Am J Respir Cell Mol Biol*, 37: 544–552. doi:10.1165/rcmb.2007-0058OC PMID:17585109
- Yao H, Guo L, Jiang BH *et al.* (2008). Oxidative stress and chromium(VI) carcinogenesis. *J Environ Pathol Toxicol Oncol*, 27: 77–88. PMID:18540844
- Yuann JM, Liu KJ, Hamilton JW, Wetterhahn KE (1999). In vivo effects of ascorbate and glutathione on the uptake of chromium, formation of chromium(V), chromium-DNA binding and 8-hydroxy-2'-deoxyguanosine in liver and kidney of osteogenic disorder shionogi rats following treatment with chromium(VI). *Carcinogenesis*, 20: 1267–1275. doi:10.1093/carcin/20.7.1267 PMID:10383900
- Zhang JD & Li XL (1987). Chromium pollution of soil and water in Jinzhou *Zhonghua Yu Fang Yi Xue Za Zhi, Chinese Journal of Preventive Medicine*, 21: 262–264. PMID:3443034
- Zhitkovich A (2005). Importance of chromium-DNA adducts in mutagenicity and toxicity of chromium(VI). *Chem Res Toxicol*, 18: 3–11. doi:10.1021/tx049774+ PMID:15651842
- Zhitkovich A, Song Y, Quievryn G, Voitkun V (2001). Non-oxidative mechanisms are responsible for the induction of mutagenesis by reduction of Cr(VI) with cysteine: role of ternary DNA adducts in Cr(III)-dependent mutagenesis. *Biochemistry*, 40: 549–560. doi:10.1021/bi0015459 PMID:11148050

NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups in 1972, 1975, 1979, 1982, 1987, and 1989 ([IARC, 1973](#), [1976](#), [1979](#), [1982](#), [1987](#), [1990](#)). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for nickel, nickel alloys, and selected nickel compounds are presented in [Table 1.1](#). This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially, and those that have been tested in biological systems. Several intermediary compounds occur in refineries that cannot be characterized, and are thus not listed.

1.2 Chemical and physical properties of the agents

Nickel (atomic number, 28; atomic weight, 58.69) is a metal, which belongs to group VIIIB of the periodic table. The most important oxidation state of nickel is +2, although the +3 and +4 oxidation states are also known ([Tundermann et al., 2005](#)). Nickel resembles iron, cobalt, and copper in its chemical properties. However,

unlike cobalt and iron, it is normally only stable in aqueous solution in the + 2 oxidation state ([Kerfoot, 2002](#)). Selected chemical and physical properties for nickel and nickel compounds, including solubility data, were presented in the previous *IARC Monograph* ([IARC, 1990](#)), and have been reported elsewhere ([ATSDR, 2005](#)).

1.3 Use of the agents

The chemical properties of nickel (i.e. hardness, high melting point, ductility, malleability, somewhat ferromagnetic, fair conductor of heat and electricity) make it suitable to be combined with other elements to form many alloys ([NTP, 2000](#); [Tundermann et al., 2005](#)). It imparts such desirable properties as corrosion resistance, heat resistance, hardness, and strength.

Nickel salts are used in electroplating, ceramics, pigments, and as intermediates (e.g. catalysts, formation of other nickel compounds). Sinter nickel oxide is used in nickel catalysts in the ceramics industry, in the manufacture of alloy steel and stainless steel, in the manufacture of nickel salts for specialty ceramics, and in the manufacture of nickel-cadmium (Ni-Cd) batteries, and nickel-metal-hydride batteries. Nickel sulfide is used as a catalyst in

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Table 1.1 Chemical names (CAS names are given in *italics*), synonyms, and molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Metallic nickel and nickel alloys			
<i>Nickel</i>	7440-02-0	C.I. 77775; Nickel element	Ni
Ferronickel	11133-76-9	<i>Iron alloy (base)</i> , <i>Fe, Ni</i> ; nickel alloy (nonbase) <i>Fe, Ni</i>	Fe, Ni
Nickel aluminium alloys	61431-86-5 37187-84-1	<i>Raney nickel</i> ; <i>Raney alloy</i>	NiAl
Nickel oxides and hydroxides			
Nickel hydroxide (amorphous)	12054-48-7 (11113-74-9)	Nickel dihydroxide; nickel (II) hydroxide; nickel (2+) hydroxide; <i>nickel hydroxide (Ni(OH)2)</i> ; nickelous hydroxide	Ni(OH) ₂
Nickel monoxide	1313-99-1 11099-02-8 34492-97-2	Black nickel oxide ^a ; green nickel oxide; mononickel oxide; nickel monooxide; nickelous oxide; <i>nickel oxide (NiO)</i> ; nickel (II) oxide; nickel (2+) oxide <i>Bunsenite (NiO)</i>	NiO
Nickel trioxide	1314-06-3	Black nickel oxidized; dinickel trioxide; nickelic oxide; nickel oxide; nickel (III) oxide; <i>nickel oxide (Ni₂O₃)</i> ; nickel peroxide; nickel sesquioxide	Ni ₂ O ₃
Nickel sulfides			
Nickel disulfide	12035-51-7 12035-50-6	<i>Nickel sulfide (NiS₂)</i> <i>Vaesite (NiS₂)</i>	NiS ₂
Nickel sulfide (amorphous)	16812-54-7 (11113-75-0)	Mononickel monosulfide; nickel mono-sulfide; nickel monosulfide (NiS); nickelous sulfide; nickel (II) sulfide; nickel (2+) sulfide;	NiS
Nickel subsulfide	1314-04-1 (61026-96-8)	<i>Nickel sulfide (NiS)</i> <i>Millerite (NiS)</i>	Ni ₃ S ₂
	12035-72-2	Nickel sesquisulfide; nickel subsulfide (Ni ₃ S ₂); <i>nickel sulfide (Ni₃S₂)</i> ; trinickel disulfide	
Pentlandite	12035-71-1	<i>Heazlewoodite (Ni₃S₂)</i> ; <i>Khizilevudite</i>	Fe ₉ Ni ₉ Si ₁₆ (Fe _{0.4-0.6} Ni _{0.4-0.6}) ₉ S ₈
	53809-86-2	Pentlandite (Fe ₉ Ni ₉ S ₁₆)	
	12174-14-0	Pentlandite	

Nickel and nickel compounds

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Nickel salts			
Nickel carbonate	3333-67-3	Carbonic acid, nickel (2+) salt (1:1); nickel carbonate (1:1); nickel (II) carbonate; nickel (2+) carbonate; nickel carbonate (NiCO ₃); nickel (2+) carbonate (NiCO ₃); nickel monocarbonate; nickelous carbonate	NiCO ₃
Basic nickel carbonates	12607-70-4	Carbonic acid, nickel salt, basic; nickel carbonate hydroxide (Ni ₃ (CO ₃)(OH) ₄); nickel, (carbonato(2-)) tetrahydroxytri-	NiCO ₃ ·2Ni(OH) ₂
	12122-15-5	Nickel bis(carbonato(2-)) hexahydroxypenta-; nickel hydroxycarbonate	2NiCO ₃ ·3Ni(OH) ₂
Nickel acetate	373-02-4	Acetic acid, nickel (2+) salt; nickel (II) acetate; nickel (2+) acetate; nickel diacetate; nickelous acetate	Ni(OCOCH ₃) ₂
Nickel acetate tetrahydrate	6018-89-9	Acetic acid, nickel (+2) salt, tetrahydrate	Ni(OCOCH ₃) ₂ ·4H ₂ O
Nickel ammonium sulfates	15-699-18-0	Ammonium nickel sulfate ((NH ₄) ₂ Ni(SO ₄) ₂); nickel ammonium sulfate (Ni(NH ₄) ₂ (SO ₄) ₂); sulfuric acid, ammonium nickel (2+) salt (2:2:1)	Ni(NH ₄) ₂ (SO ₄) ₂
Nickel ammonium sulfate hexahydrate	25749-08-0	Ammonium nickel sulfate ((NH ₄) ₂ Ni(SO ₄) ₂); sulfuric acid, ammonium nickel (2+) salt (3:2:2)	Ni ₂ (NH ₄) ₂ (SO ₄) ₃
	7785-20-8	Ammonium nickel (2+) sulfate hexahydrate; ammonium nickel sulfate ((NH ₄) ₂ Ni(SO ₄) ₂); diammonium nickel disulfate hexahydrate; diammonium nickel (2+) disulfate hexahydrate; nickel ammonium sulfate (Ni(NH ₄) ₂ (SO ₄) ₂) hexahydrate; nickel diammonium disulfate hexahydrate; sulfuric acid, ammonium nickel (2+) salt (2:2:1), hexahydrate	Ni(NH ₄) ₂ (SO ₄) ₂ ·6H ₂ O
Nickel chromate	14721-18-7	Chromium nickel oxide (NiCrO ₄); nickel chromate (NiCrO ₄); nickel chromium oxide (NiCrO ₄)	NiCrO ₄
Nickel chloride	7718-54-9	Nickel (II) chloride; nickel (2+) chloride; nickel chloride (NiCl ₂); nickel dichloride; nickel dichloride (NiCl ₂); nickelous chloride	NiCl ₂
Nickel chloride hexahydrate	7791-20-0	Nickel chloride (NiCl ₂) hexahydrate	NiCl ₂ ·6H ₂ O
Nickel nitrate hexahydrate	13478-00-7	Nickel (2+) bis(nitrate)hexahydrate; nickel dinitrate hexahydrate; nickel (II) nitrate hexahydrate; nickel nitrate (Ni(NO ₃) ₂) hexahydrate; nickelous nitrate hexahydrate; nitric acid, nickel (2+) salt, hexahydrate	Ni(NO ₃) ₂ ·6H ₂ O
Nickel sulfate	7786-81-4	Nickel monosulfate; nickelous sulfate; nickel sulfate (1:1); nickel (II) sulfate; nickel (2+) sulfate; nickel (2+) sulfate (1:1); nickel sulfate (NiSO ₄); sulfuric acid, nickel (2+) salt (1:1)	NiSO ₄
Nickel sulfate hexahydrate	10101-97-0	Sulfuric acid, nickel (2+) salt (1:1), hexahydrate	NiSO ₄ ·6H ₂ O
Nickel sulfate heptahydrate	10101-98-1	Sulfuric acid, nickel (2+) salt (1:1), heptahydrate	NiSO ₄ ·7H ₂ O

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Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Other nickel compounds			
Nickel carbonyl	13463-39-3	<i>Nickel carbonyl</i> ($\text{Ni}(\text{CO})_4$), (<i>T-4</i>); nickel tetracarbonyl; tetracarbonylnickel; tetracarbonylnickel (0)	$\text{Ni}(\text{CO})_4$
Nickel antimonide	12035-52-8	<i>Antimony compound with nickel</i> (1:1); nickel antimonide (NiSb); nickel compound with antimony (1:1); nickel monoantimonide	NiSb
Nickel arsenides	12125-61-0	<i>Breithauptite</i> (SbNi)	
	27016-75-7	<i>Nickel arsenide</i> (NiAs)	NiAs
	1303-13-5	Nickeline; <i>nickeline</i> (NiAs); niccolite	NiAs
	12256-33-6	<i>Nickel arsenide</i> ($\text{Ni}_{11}\text{As}_8$); nickel arsenide tetragonal	$\text{Ni}_{11}\text{As}_8$
	12044-65-4	<i>Maucherite</i> ($\text{Ni}_{11}\text{As}_8$); Placodine; Temiskamite	$\text{Ni}_{11}\text{As}_8$
Nickel selenide	12255-80-0	<i>Nickel arsenide</i> (Ni_5As_2); nickel arsenide hexagonal	Ni_5As_2
	1314-05-2	Nickel monoselenide; <i>nickel selenide</i> (NiSe)	NiSe
	12201-85-3	Maekinenite; <i>Makinenite</i> (NiSe)	
	12137-13-2	<i>Nickel selenide</i> (Ni_3Se_2)	Ni_3Se_2
	12255-10-6	<i>Nickel arsenide sulfide</i> (NiAsS)	NiAsS
Nickel sulfarsenide	12255-11-7	<i>Gersdorffite</i> (NiAsS)	
Nickel telluride	12142-88-0	Nickel monotelluride; <i>nickel telluride</i> (NiTe)	NiTe
	24270-51-7	<i>Imgreite</i> (NiTe)	
Nickel titanate	12035-39-1	Nickel titanate(IV); nickel titanate (Ni-TiO ₃); <i>nickel titanium oxide</i> (NiTiO ₃); nickel titanium trioxide	NiTiO ₃
Chrome iron nickel black spinel	71631-15-7	CI: 77 504; <i>CI Pigment Black 30</i> ; nickel iron chromite black spinel	(Ni,Fe)(CrFe) ₂ O ₄ NS
Nickel ferrite brown spinel	68187-10-0	<i>CI Pigment Brown 34</i>	NiFe ₂ O ₄
Nickelocene	1271-28-9	Bis(η^5 -2,4-cyclopentadien-1-yl)nickel; di- π -cyclopentadienylnickel; dicyclopentadienyl-nickel; bis(η^5 -2,4-cyclopentadien-1-yl)-nickel	π -(C ₅ H ₅) ₂ Ni

^a In commercial usage, 'black nickel oxide' usually refers to the low-temperature crystalline form of nickel monoxide, but nickel trioxide (Ni₂O₃), an unstable oxide of nickel, may also be called 'black nickel oxide'.

the petrochemical industry or as an intermediate in the metallurgical industry.

According to the US Geological Survey, world use of primary nickel in 2006 was 1.40 million tonnes, a 12% increase over 2005. Stainless steel manufacture accounted for more than 60% of primary nickel consumption in 2006 ([USGS, 2008](#)). Of the 231000 tonnes of primary nickel consumed in the USA in 2007, approximately 52% was used in stainless and alloy steel production, 34% in non-ferrous alloys and superalloys, 10% in electroplating, and 4% in other uses. End uses of nickel in the USA in 2007 were as follows: transportation, 30%; chemical industry, 15%; electrical equipment, 10%; construction, 9%; fabricated metal products, 8%; household appliances, 8%; petroleum industry, 7%; machinery, 6%; and others, 7% ([Kuck, 2008](#)).

1.3.1 Metallic nickel and nickel alloys

Pure nickel metal is used to prepare nickel alloys (including steels). It is used as such for plating, electroforming, coinage, electrical components, tanks, catalysts, battery plates, sintered components, magnets, and welding rods. Ferronickel is used to prepare steels. Stainless and heat-resistant steels accounted for 93% of its end-use in 1986. Nickel-containing steels with low nickel content (< 5%) are used in construction and tool fabrication. Stainless steels are used in general engineering equipment, chemical equipment, domestic applications, hospital equipment, food processing, architectural panels and fasteners, pollution-control equipment, cryogenic uses, automotive parts, and engine components ([IARC, 1990](#)).

Nickel alloys are often divided into categories depending on the primary metal with which they are alloyed (e.g. iron, copper, molybdenum, chromium) and their nickel content. Nickel is alloyed with iron to produce alloy steels (containing 0.3–5% nickel), stainless steels (containing as much as 25–30% nickel, although 8–10% nickel

is more typical), and cast irons. Nickel–copper alloys (e.g. Monel alloys) are used for coinage (25% nickel, 75% copper), industrial plumbing (e.g. piping and valves), marine equipment, petrochemical equipment, heat exchangers, condenser tubes, pumps, electrodes for welding, architectural trim, thermocouples, desalination plants, ship propellers, etc. Nickel–chromium alloys (e.g. Nichrome) are used in many applications that require resistance to high temperatures such as heating elements, furnaces, jet engine parts, and reaction vessels. Molybdenum-containing nickel alloys and nickel–iron–chromium alloys (e.g. Inconel) provide strength and corrosion resistance over a wide temperature range, and are used in nuclear and fossil-fuel steam generators, food-processing equipment, and chemical-processing and heat-treating equipment. Hastelloy alloys (which contain nickel, chromium, iron, and molybdenum) provide oxidation and corrosion resistance for use with acids and salts. Nickel-based super-alloys provide high-temperature strength and creep, and stress resistance for use in gas-turbine engines ([ATSDR, 2005](#)).

Other groups of nickel alloys are used according to their specific properties for acid-resistant equipment, heating elements for furnaces, low-expansion alloys, cryogenic uses, storage of liquefied gases, high-magnetic-permeability alloys, and surgical implant prostheses.

1.3.2 Nickel oxides and hydroxides

The nickel oxide sinters are used in the manufacture of alloy steels and stainless steels.

Green nickel oxide is a finely divided, relatively pure form of nickel monoxide, produced by firing a mixture of nickel powder and water in air at 1000 °C ([IARC, 1990](#)). It is used to manufacture nickel catalysts and specialty ceramics (for porcelain enamelling of steel; in the manufacture of magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes; and

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as a colourant in glass and ceramic stains used in ceramic tiles, dishes, pottery, and sanitary ware).

Black nickel oxide is a finely divided, pure nickel monoxide, produced by calcination of nickel hydroxycarbonate or nickel nitrate at 600 °C; nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called ‘black nickel oxide’ ([IARC, 1990](#)). Black nickel oxide is used in the manufacture of nickel salts, specialty ceramics, and nickel catalysts (e.g. to enhance the activity of three-way catalysts containing rhodium, platinum, and palladium used in automobile exhaust control).

Nickel hydroxide is used as a catalyst intermediate, and in the manufacture of Ni–Cd batteries ([Antonsen & Meshri, 2005](#)).

1.3.3 Nickel sulfides

Nickel sulfide is used as a catalyst in petrochemical hydrogenation when high concentrations of sulfur are present in the distillates. The major use of nickel monosulfide is as an intermediate in the hydrometallurgical processing of silicate-oxide nickel ores ([IARC, 1990](#)). Nickel subsulfide is used as an intermediate in the primary nickel industry ([ATSDR, 2005](#)).

1.3.4 Nickel salts

Nickel acetate is used in electroplating, as an intermediate (e.g. as catalysts and in the formation of other nickel compounds), as a dye mordant, and as a sealer for anodized aluminium.

Nickel carbonate is used in the manufacture of nickel catalysts, pigments, and other nickel compounds (e.g. nickel oxide, nickel powder); in the preparation of coloured glass; and, as a neutralizing compound in nickel-electroplating solutions.

Nickel ammonium sulfate is used as a dye mordant, in metal-finishing compositions, and as an electrolyte for electroplating.

Nickel chloride is used as an intermediate in the manufacture of nickel catalysts, and to absorb ammonia in industrial gas masks.

Nickel nitrate hexahydrate is used as an intermediate in the manufacture of nickel catalysts and Ni–Cd batteries.

Nickel sulfate hexahydrate is used in nickel electroplating and nickel electrorefining, in ‘electroless’ nickel plating, and as an intermediate (in the manufacture of other nickel chemicals and catalysts) ([Antonsen & Meshri, 2005](#)).

1.3.5 Other nickel compounds

The primary use for nickel carbonyl is as an intermediate (in the production of highly pure nickel), as a catalyst in chemical synthesis, as a reactant in carbonylation reactions, in the vapour-plating of nickel, and in the fabrication of nickel and nickel alloy components and shapes.

Nickelocene is used as a catalyst and complexing agent, and nickel titanate is used as a pigment ([Antonsen & Meshri, 2005](#)).

No information was available to the Working Group on the use of nickel selenides or potassium nickelocyanate.

1.4 Environmental occurrence

Nickel and its compounds are naturally present in the earth’s crust, and are emitted to the atmosphere via natural sources (such as windblown dust, volcanic eruptions, vegetation forest fires, and meteoric dust) as well as from anthropogenic activities (e.g. mining, smelting, refining, manufacture of stainless steel and other nickel-containing alloys, fossil fuel combustion, and waste incineration). Estimates for the emission of nickel into the atmosphere from natural sources range from 8.5 million kg/year in the 1980s to 30 million kg/year in the early 1990s ([ATSDR, 2005](#)). The general population is exposed to low levels of nickel in ambient air, water, food, and through tobacco consumption.

1.4.1 Natural occurrence

Nickel is widely distributed in nature and is found in animals, plants, and soil ([EVM, 2002](#)). It is the 24th most abundant element, forming about 0.008% of the earth's crust (0.01% in igneous rocks). The concentration of nickel in soil is approximately 79 ppm, with a range of 4–80 ppm ([EVM, 2002](#); [ATSDR, 2005](#)).

1.4.2 Air

Nickel is emitted to the atmosphere from both natural and anthropogenic sources. It has been estimated that approximately 30000 tonnes of nickel may be emitted per year to the atmosphere from natural sources. The anthropogenic emission rate is estimated to be between 1.4–1.8 times higher than the natural emission rate.

The two main natural sources are volcanoes and windblown dust from rocks and soil, estimated to respectively contribute 14000 tonnes/year and 11000 tonnes/year ([NTP, 2000](#); [Barbante et al., 2002](#)). Other relatively minor sources include: wild forest fires (2300 tonnes/year), sea salt spray (1300 tonnes/year), continental particulates (510 tonnes/year), marine (120 tonnes/year), and continental volatiles (100 tonnes/year) ([Barbante et al., 2002](#)).

Anthropogenic activities release nickel to the atmosphere, mainly in the form of aerosols ([ATSDR, 2005](#)). Fossil fuel combustion is reported to be the major contributor of atmospheric nickel in Europe and the world, accounting for 62% of anthropogenic emissions in the 1980s ([Barbante et al., 2002](#); [ATSDR, 2005](#)). In 1999, an estimated 570000 tons of nickel were released from the combustion of fossil fuels worldwide ([Rydh & Svärd, 2003](#)). Of this, 326 tons were released from electric utilities ([Leikauf, 2002](#)). Of the other anthropogenic sources, nickel metal and refining accounted for 17% of total emissions, municipal incineration 12%, steel production 3%, other

nickel-containing alloy production 2%, and coal combustion 2% ([ATSDR, 2005](#)).

Atmospheric nickel concentrations are higher in rural and urban air (concentration range: 5–35 ng/m³) than in remote areas (concentration range: 1–3 ng/m³) ([WHO, 2007](#)).

1.4.3 Water

Particulate nickel enters the aquatic environment from a variety of natural and anthropogenic sources. Natural sources include the weathering and dissolution of nickel-containing rocks and soil, disturbed soil, and atmospheric deposition. Anthropogenic sources include: industrial processes (e.g. mining and smelting operations), industrial waste water and effluent (e.g. tailings piles run-off), domestic waste water, and land-fill leachate ([NTP, 2000](#); [ATSDR, 2005](#); [WHO, 2007](#)). Several factors influence the concentration of nickel in groundwater and surface water including: soil use, pH, and depth of sampling ([WHO, 2007](#)). Most nickel compounds are relatively water soluble at low pH (i.e. pH < 6.5). As a result, acid rain tends to increase the mobility of nickel in soil, which, in turn, has a corresponding impact on nickel concentrations in groundwater ([NTP, 2000](#); [WHO, 2007](#)).

Based on measurement data from the 1980s, the following average nickel concentrations have been reported for groundwater, seawater and surface water, respectively: <20 µg/L, 0.1–0.5 µg/L, and 15–20 µg/L ([NTP, 2000](#); [ATSDR, 2005](#)). Nickel concentrations as high as 980 µg/L have been measured in groundwater with pH < 6.2 ([WHO, 2007](#)). Levels of dissolved nickel ranging from < 1–87 µg/L have been reported in urban storm run-off water samples ([ATSDR, 2005](#)).

Nickel concentrations in the range of 6–700 pg/g have been measured in high-altitude snow and ice near the summit of Mont Blanc on the French-Italian border. Seasonal variations were observed, with higher concentrations in the summer layers than in the winter layers.

Nickel levels appeared to be more associated with anthropogenic inputs (e.g. oil combustion from power generation, automobile and truck traffic) than with natural sources, such as rock and soil dust ([Barbante et al., 2002](#)).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mining and smelting, coal fly ash, bottom ash, metal manufacturing waste, commercial waste, atmospheric fall-out and deposition, urban refuse, and sewage sludge) contribute to the levels of nickel found in soil and sediments ([NTP, 2000](#); [ATSDR, 2005](#)). Of the nickel emitted to the environment, the largest releases are to the soil. In 2002, estimated releases of nickel and nickel compounds from manufacturing and processing facilities (required to report to the US Toxic Release Inventory Program) were approximately 5530 and 14800 metric tonnes, respectively—accounting for 82% and 87% of estimated total nickel releases to the environment ([ATSDR, 2005](#)).

In a study of urban soil quality, a harmonized sampling regime was used to compare concentrations of nickel in six European cities differing markedly in their climate and industrial history. The sites were as far as possible from current point sources of pollution, such as industrial emissions, but all were bordered by major roads, and are thus likely to have been affected by vehicle emissions. To assess the vertical distribution of soil parameters, two depths were sampled at each point: a surface sample at 0–10 cm and a subsurface sample at 10–20 cm. The surface sample mean nickel concentration was in the range of 11–207 mg/kg, and the corresponding mean concentration in the subsurface sample, 10–210 mg/kg ([Madrid et al., 2006](#)).

1.5 Human exposure

1.5.1 Exposure of the general population

Ingestion of nickel in food, and to a lesser degree in drinking-water, is the primary route of exposure for the non-smoking general population. Exposure may also occur via inhalation of ambient air and percutaneous absorption ([NTP, 2000](#); [ATSDR, 2005](#); [WHO, 2007](#)). The daily intake of nickel from food and beverages varies by foodstuff, by country, by age, and by gender ([EVM, 2002](#); [ATSDR, 2005](#)). Data from a study in the USA give estimates of daily dietary intakes in the range of 101–162 µg/day for adults, 136–140 µg/day for males, and 107–109 µg/day for females. Estimates for pregnant and lactating women are higher with average daily intakes of 121 µg/day and 162 µg/day, respectively ([ATSDR, 2005](#)). Based on the concordance between different studies of dietary intake, diet is reported to contribute less than 0.2 mg/day ([WHO, 2007](#)).

Inhalation of nickel from ambient air is generally a minor route of exposure for the general population. The following daily intakes of nickel have been estimated: less than 0.05 µg/day in the USA; 0.42 µg/day (mean ambient concentration) and 15 µg/day (highest ambient concentration) in the Sudbury basin region in Ontario, Canada; and, 122 µg/day (based on the highest ambient reported nickel concentration) in the Copper Cliff region of Ontario, Canada. These estimates are based on a breathing rate of 20 m³/day, and nickel concentrations of 2.2 ng/m³, 21 ng/m³, 732 ng/m³, and 6100 ng/m³, respectively ([ATSDR, 2005](#)).

1.5.2 Occupational exposure

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin

contact occur in nickel-producing industries (e.g. mining, milling, smelting, and refining), as well as in nickel-using industries and operations (e.g. alloy and stainless steel manufacture; electroplating and electrowinning; welding, grinding and cutting). Insoluble nickel is the predominant exposure in nickel-producing industries, whereas soluble nickel is the predominant exposure in the nickel-using industries. Occupational exposure results in elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake ([IARC, 1990](#); [NTP, 2000](#)).

Estimates of the number of workers potentially exposed to nickel and nickel compounds have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–1983, NIOSH estimated that 507681 workers, including 19673 female workers, were potentially exposed to ‘Ni, Nickel-MF Unknown’ (agent code: 50420) in the workplace ([NIOSH, 1990](#)). The following six industries accounted for nearly 60% of exposed workers: ‘fabricated metal products’ ($n = 69984$), ‘special trade contractors’ ($n = 55178$), ‘machinery, except electrical’ ($n = 55064$), ‘transportation equipment’ ($n = 44838$), ‘primary metal industries’ ($n = 39467$), and ‘auto repair, services, and garages’ ($n = 27686$). Based on occupational exposure to known and suspected carcinogens collected during 1990–1993, the CAREX database estimates that 547396 workers were exposed to nickel and nickel compounds in the European Union. Over 83% of these workers were employed in the ‘manufacture of fabricated metal products, except machinery and equipment’ ($n = 195597$), ‘manufacture of machinery, except electrical’ ($n = 122985$), ‘manufacture of transport equipment’ ($n = 64720$), ‘non-ferrous base metal industries’ ($n = 32168$), ‘iron and steel basic industries’ ($n = 26504$), and ‘metal ore mining’ ($n = 16459$). [CAREX Canada \(2011\)](#)

estimates that approximately 50000 Canadians are exposed to nickel in the workplace (95% male). Exposed industries include: commercial/ industrial machinery and equipment repair/ maintenance; architectural, structural metals manufacturing; specialty trade contractors; boiler, tank and shipping container manufacturing; metal ore mining; motor vehicle parts manufacturing; machine shops, turned product, screw, nut and bolt manufacturing; coating, engraving, heat treating and allied activities; iron/steel mills and ferro-alloy manufacturing; non-ferrous metal production and processing.

Historically, metallic nickel exposures tended to be higher in nickel-producing industries than in the nickel-using industries, with estimates of historical mean levels of exposure to inhalable metallic nickel in the range of 0.01–6.0 mg/m³ and 0.05–0.3 mg/m³, respectively. However, data from the EU suggest that occasional higher exposures to inhalable metallic nickel may be present in certain industry sectors ([Sivulka, 2005](#)).

Data on early occupational exposures to nickel and nickel compounds were summarized in the previous *IARC Monograph* ([IARC, 1990](#)). Data from studies and reviews on nickel exposure published since the previous *IARC Monograph* are summarized below for both the nickel-producing and the nickel-using industries.

(a) *Studies of nickel-producing industries*

[Ulrich et al. \(1991\)](#) collected data on several indicators of nickel exposure (stationary and personal air sampling; urinary nickel excretion) among electrolytic nickel production workers in the Czech Republic (formerly, Czechoslovakia). Air samples ($n = 52$) were collected on membrane filters and analysed by electrothermal atomic absorption spectrometry. Urine samples ($n = 140$) were collected during the last 4 hours of workers’ shifts, and the results were corrected to a standard density of 1.024. In a matched-pair analysis of air and urine samples collected from 18 electrolysis workers, the correlation coefficient

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was 0.562; the mean concentration of nickel in urine was 53.3 $\mu\text{g/L}$ (range, 1.73–98.55 $\mu\text{g/L}$), and the mean concentration in air was 0.187 mg/m^3 (range, 0.002–0.481 mg/m^3).

In a study conducted at a Finnish electrolytic nickel refinery, [Kiilunen et al. \(1997\)](#) collected data on nickel concentrations in air, blood, and urine. Stationary samples ($n = 141$) were collected from 50 locations in the refinery, including those areas where breathing zone samples were taken. Personal (i.e. 8-hour breathing zone) samples were collected over 4 successive work days ($n = 157$), from the shoulders when no respiratory protection was worn, inside the mask when protective equipment was worn, and inside the mask hanging on the shoulder of the worker when the mask was taken off. Historical occupational hygiene measurements were examined to assess past exposure. Spot urine samples ($n = 154$) were collected, pre- and post-shift, over 4 successive work days and 1 free day thereafter. Blood samples ($n = 64$) were collected at the beginning of the study and at the end of the last work shift. A total of 34 workers (of 100) volunteered to participate in the study. Urinary nickel results in the workers were compared with two non-exposed control groups (30 office workers from the refinery and 32 unexposed persons from the Helsinki area). For the stationary samples, nickel concentrations were reported by location as water-soluble nickel, acid-soluble nickel and total nickel (all in $\mu\text{g/m}^3$). Geometric mean nickel concentrations ranged from: 7.4 $\mu\text{g/m}^3$ ('other sites') to 451 $\mu\text{g/m}^3$ (in 'tank house 3') for water-soluble nickel; 0.5 $\mu\text{g/m}^3$ ('other sites') to 4.6 $\mu\text{g/m}^3$ ('solution purification') for acid-soluble nickel; and, 7.6 $\mu\text{g/m}^3$ ('other sites') to 452 $\mu\text{g/m}^3$ (in 'tank house 3'). For the breathing zone samples, the range of geometric mean nickel concentrations was 0.2–3.2 $\mu\text{g/m}^3$ (inside the mask) and 0.6–63.2 $\mu\text{g/m}^3$ (no mask). Based on a review of historical stationary sampling data, average nickel concentrations varied in the range of 230–800 $\mu\text{g/m}^3$ over the period 1966–88.

Lower concentrations (112–484 $\mu\text{g/m}^3$) were observed in the early 1990s. Geometric mean after-shift urinary concentrations of nickel were in the range of 0.1–0.8 $\mu\text{mol/L}$ (mask in use) and 0.5–1.7 $\mu\text{mol/L}$ (no mask in use). Urinary nickel concentrations were still elevated after 2- and 4-week vacations. No consistent correlations between airborne nickel concentrations and nickel concentrations in the blood or urine were observed.

[Thomassen et al. \(2004\)](#) measured the exposure of 135 copper refinery workers (45 females, 90 males) to copper, nickel and other trace elements at a nickel refinery complex in Monchegorsk, the Russian Federation. Full-shift breathing zone samples were collected for workers in the pyrometallurgical process ($n = 138$) and in the electrorefining process ($n = 123$) areas. Workers wore personal samplers for two to four full shifts. IOM samplers were used to assess the inhalable aerosol fraction, and Respicon samplers (3-stage virtual impactors) were used to separate the inhalable fraction into respirable, tracheobronchial, and extrathoracic aerosol fractions. The geometric mean inhalable nickel concentration was in the range of 0.024–0.14 mg/m^3 for samples taken in the pyrometallurgical areas, and 0.018–0.060 mg/m^3 for samples taken in the electrorefining areas (data presented as the sum of the inhalable water-soluble and water-insoluble subfractions). For the inhalable aerosol nickel concentrations observed in the pyrometallurgical process steps, the water-insoluble subfraction contained higher levels than the water-soluble fraction, with geometric means of 59 $\mu\text{g/m}^3$ and 14 $\mu\text{g/m}^3$, respectively. In the electrorefining process area, the nickel concentrations in the inhalable subfractions were 14 $\mu\text{g/m}^3$ (water-soluble) and 10 $\mu\text{g/m}^3$ (water-insoluble).

Air monitoring was conducted in three areas of a nickel base metal refinery in South Africa (the ball mill area, the copper winning area, and the nickel handling area). Personal breathing zone samples ($n = 30$) were collected in all areas of the

plant, and were analysed gravimetrically and by inductively coupled plasma mass spectroscopy. The mean time-weighted average concentrations for soluble, insoluble and total nickel dust, respectively, were 44, 51, and 95 $\mu\text{g}/\text{m}^3$ in the ball mill area; 395, 400, and 795 $\mu\text{g}/\text{m}^3$ in the nickel handling area; and 46, 17, and 63 $\mu\text{g}/\text{m}^3$ in the copper winning area ([Harmse & Engelbrecht, 2007](#)).

Airborne dust concentrations, nickel concentrations, nickel speciation, and aerosol particle size distributions in two large-scale nickel production facilities were assessed by collecting a total of 46 inhalable samples (30 personal, 16 area), and 28 cascade impactor samples (18 personal, 10 area). Samples were collected using IOM and Marple cascade impactor sampling heads, and analysed gravimetrically. At the first site, inhalable concentrations were in the range of 0.5–9.1 mg/m^3 for the personal samples, and 0.2–5.7 mg/m^3 for the area samples (median concentrations, 0.7 mg/m^3 and 0.4 mg/m^3 , respectively). Total nickel levels in the personal samples were in the range of 1.8–814.9 $\mu\text{g}/\text{m}^3$, and 19.8–2481.6 $\mu\text{g}/\text{m}^3$ in the area samples (median concentrations, 24.6 $\mu\text{g}/\text{m}^3$ and 92.0 $\mu\text{g}/\text{m}^3$, respectively). At the second site, airborne concentrations of inhalable dust were in the range of 1.2–25.2 mg/m^3 for the personal samples, and 1.5–14.3 mg/m^3 (median concentrations, 3.8 mg/m^3 and 2.9 mg/m^3 , respectively) for the area samples. Total nickel levels were in the range of 36.6–203.4 $\mu\text{g}/\text{m}^3$ in the area samples, and 0.2–170.7 $\mu\text{g}/\text{m}^3$ in the personal samples (median concentrations, 91.3 and 15.2 $\mu\text{g}/\text{m}^3$, respectively) ([Creely & Aitken, 2008](#)).

(b) *Studies of nickel-using industries*

[Bavazzano et al. \(1994\)](#) collected air, face, hand, and spot urine samples from 41 male workers in electroplating operations in 25 small factories in the province of Florence, Italy, and compared them to samples collected from non-exposed male subjects (face and hand samples: $n = 15$ subjects aged 15–60 years old; urine

samples: $n = 60$ subjects aged 22–63 years old). For the airborne nickel measurements, personal exposure were in the range of 0.10–42 $\mu\text{g}/\text{m}^3$ (median concentration, 2.3 $\mu\text{g}/\text{m}^3$). The median nickel levels in the urine, on the hands, and on the face were, respectively, 4.2 $\mu\text{g}/\text{L}$ (range, 0.7–50 $\mu\text{g}/\text{L}$), 39 μg (range, 1.9–547 μg), and 9.0 μg (range, 1.0–86 μg). Median hand, face, and urine nickel levels for the control subjects were, respectively, 0.8 μg (range, 0.0–5.3 μg ; $n = 15$), 0.30 μg (range, 0.0–2.4; $n = 15$), and 0.7 μg (range, 0.1–2.5 μg ; $n = 60$).

In an occupational hygiene survey of 38 nickel electroplating shops in Finland, exposure to nickel was assessed by questionnaire ($n = 163$), urine samples (phase 1: $n = 145$; phase 2: $n = 104$), bulk samples ($n = 30$), and air measurements in three representative shops (one clean, one intermediate, one dirty) on 1 day during which urine samples were also being collected. Full-shift breathing zone samples were collected from inside and outside a respirator with filters. In the first phase of the study, average urinary nickel concentration was 0.16 $\mu\text{mol}/\text{L}$ (range, 0.0–5.0 $\mu\text{mol}/\text{L}$; $n = 145$). The range of mean values for different workplaces was 0.01–0.89 $\mu\text{mol}/\text{L}$, and for the median values, 0.02–0.05 $\mu\text{mol}/\text{L}$. For the 97 workers followed in the second phase, urinary nickel concentrations were observed to fluctuate with exposure, with mean nickel concentrations in the range of 0.10–0.11 $\mu\text{mol}/\text{L}$ for the morning specimens, and 0.12–0.16 $\mu\text{mol}/\text{L}$ for the afternoon specimens. Personal breathing zone nickel concentrations were as follows: 0.5 $\mu\text{g}/\text{m}^3$ (hanger worker in the ‘clean shop’), 0.7 $\mu\text{g}/\text{m}^3$ (worker responsible for maintenance of nickel bath in the ‘clean’ shop), and in the range of 5.6–78.3 $\mu\text{g}/\text{m}^3$ for workers ($n = 6$) in the ‘dirty’ shop. In the area samples, nickel concentrations were 26 $\mu\text{g}/\text{m}^3$ (near the nickel bath in the ‘clean’ shop), 11.9–17.8 $\mu\text{g}/\text{m}^3$ (in the hanging area of the ‘dirty’ shop), and 73.3 $\mu\text{g}/\text{m}^3$ (beside the nickel bath in the ‘dirty’ shop) ([Kiilunen et al., 1997](#)).

[Kiilunen \(1997\)](#) analysed data from the biomonitoring registry and the occupational hygiene service registry of the Finnish Institute of Occupational Health to examine trends in nickel exposure during 1980–89. A total of 1795 urinary nickel samples (for which it was possible to identify job titles) were examined, along with 260 nickel measurements from the breathing zone of workers for whom job titles were available. Across all job titles, the ranges of mean urinary nickel concentrations, by time period, were as follows: 0.05–0.52 $\mu\text{mol/L}$ for 1980–82, 0.14–0.51 $\mu\text{mol/L}$ for 1983–85, and 0.17–0.87 $\mu\text{mol/L}$ for 1986–89. The two largest occupational groups sampled were platers ($n = 503$), and welders ($n = 463$). Mean urinary concentrations for platers, by time period, were 0.35 $\mu\text{mol/L}$ for 1980–82 (range, 0.01–2.95), 0.30 $\mu\text{mol/L}$ for 1983–85 (range, 0.01–2.10), and 0.38 $\mu\text{mol/L}$ for 1986–89 (range, 0.03–2.37). Mean urinary concentrations for welders, by time period, were 0.22 $\mu\text{mol/L}$ for 1980–82 (range, 0.03–1.58), 0.17 $\mu\text{mol/L}$ for 1983–85 (range, 0.03–0.65), and 0.21 $\mu\text{mol/L}$ for 1986–89 (range, 0.01–1.58). Analysis of the breathing zone measurements revealed that 22.1% of all measurements in 1980–82 had exceeded the occupational exposure limit (OEL) of 0.1 mg/m^3 . Similar results were seen for the 1983–85 period (24.8%), rising to 30.7% for the 1986–89 period. Job titles with mean values over the OEL in 1983–85 included: grinders (mean, 0.76 mg/m^3 , $n = 29$), one metal worker (0.12 mg/m^3), powder cutters (mean, 0.34 mg/m^3 , $n = 31$), one spray painter (0.20 mg/m^3), and welders (0.17 mg/m^3 , $n = 72$). Mean levels exceeded the OEL in the following four occupational groups during 1986–89: carbon arc chisellers (mean, 0.6 mg/m^3 , $n = 2$), grinders (mean, 0.28 mg/m^3 , $n = 19$), one warm handler (0.18 mg/m^3), and burn cutters (mean, 0.14 mg/m^3 , $n = 2$).

The association between occupational exposure to airborne nickel and nickel absorption was examined by collecting personal breathing zone samples and urine samples from 10 workers

at a galvanizing plant in Brazil that uses nickel sulfate. Spot urine samples were collected pre- and post-shift from the nickel-exposed workers over 5 consecutive days, and from 10 non-nickel exposed workers employed at a zinc plant over 3 consecutive days ($n = 97$ and 55, respectively). Both groups completed a questionnaire on occupational history, health and lifestyle factors; exposed workers also underwent a medical examination. Personal breathing zone samples (first 4 hours of shift) were collected using NIOSH protocols. Geometric mean airborne nickel levels were in the range of 2.8–116.7 $\mu\text{g/m}^3$, and the urine levels, from samples taken post-shift, were in the range of 4.5–43.2 $\mu\text{g/g}$ creatinine (mean, 14.7 $\mu\text{g/g}$ creatinine) ([Oliveira et al., 2000](#)).

[Sorahan \(2004\)](#) examined data on mean (unadjusted) levels of exposure to inhalable nickel at a nickel alloy plant during 1975–2001 in Hereford, the United Kingdom. Data were reported for two time periods: 1975–80 and 1997–2001. Mean nickel levels (unadjusted) for the earlier period were as follows: 0.84 mg/m^3 in the melting, fettling, and pickling areas; 0.53 mg/m^3 in the extrusion and forge, hot strip and rolling, engineering, and melting stores areas; 0.55 mg/m^3 in the machining, hot rolling, Nimonic finishing, and craft apprentice areas; 0.40 mg/m^3 in the roll turning and grinding, cold rolling, cold drawing, wire drawing, and inspection areas; and 0.04 mg/m^3 in the process stock handling, distribution and warehouse areas. The corresponding mean nickel levels (unadjusted) for the latter period were: 0.37 mg/m^3 , 0.45 mg/m^3 , 0.31 mg/m^3 , 0.30 mg/m^3 , and 0.29 mg/m^3 , respectively.

Eight-hour TWA (8-h TWA) exposures calculated for the period 1997–2001 were 0.33 mg/m^3 , 0.31 mg/m^3 , 0.16 mg/m^3 , 0.16 mg/m^3 , and 0.27 mg/m^3 , respectively.

[Sorahan & Williams \(2005\)](#) assessed the mortality of workers at a nickel carbonyl refinery in Clydach, the United Kingdom to determine whether occupational exposure to nickel resulted in increased risks of nasal cancer and lung cancer.

Using personal sampling data collected in the 1980s and 1990s, 8-h TWA exposure to total inhalable nickel was calculated, and assigned to six categories of work, based on the predominant species of nickel exposure. The six categories of work were: feed handling and nickel extraction, including kilns (oxide/metallic); pellet and powder production, and shipping (metallic); nickel salts and derivatives, and effluent (metallic/soluble); wet treatment and related processes (metallic/subsulfide/soluble); gas plant (non-nickel); and engineering and site-wide activities that could include any of the preceding work areas. Mean levels of total inhalable nickel dust were in the range of 0.04–0.57 mg/m³ in the 1980s ($n = 1781$), and 0.04–0.37 mg/m³ in the 1990s ($n = 1709$).

[Stridsklev et al. \(2007\)](#) examined the relationship between the concentration of airborne nickel in the occupational environment of grinders ($n = 9$) grinding stainless steel in Norway and the concentration of nickel in their urine and blood. Grinders either worked in a well ventilated hall of a shipyard or in a small non-ventilated workshop. The sampling protocol was as follows: full-shift personal samples were collected in the breathing zone of grinders over the course of 1 work week; urine samples were collected three times daily for 1 week (first void in the morning, pre- and post-shift); and blood samples were drawn twice daily for 3 days in 1 week (pre- and post-shift). Blood and urine samples were also collected on the Monday morning after a 3-week vacation in the workshop. Grinders also completed a questionnaire to collect information on work history, use of personal protective equipment, and smoking habits. Mean levels of airborne nickel were 18.9 µg/m³ (range, 1.8–88.6 µg/m³) in the shipyard, and 249.8 µg/m³ (range, 79.5–653.6 µg/m³) in the workshop. Mean blood nickel levels for grinders were 0.87 µg/L (range, < 0.8–2.4 µg/L) in whole blood, and 1.0 µg/L (range, < 0.4–4.1 µg/L) in plasma. Mean urinary nickel levels for grinders were 3.79 µg/g creatinine (range, 0.68–10.6 µg/g creatinine), 3.39 µg/g

creatinine (range, 0.25–11.1 µg/g creatinine), and 4.56 µg/g creatinine (range, < 0.53–11.5 µg/g creatinine), from the first void, pre- and post-shift samples, respectively. With the exception of stainless steel welders welding the MIG/MAG-method [Metal Inert Gas-Metal Active Gas], mean urinary nickel levels were higher in grinders than in welders. Mean urinary nickel levels in MIG/MAG welders were 5.9 µg/g creatinine (range, < 0.24–20.5 µg/g creatinine), 3.8 µg/g creatinine (range, 0.33–11.4 µg/g creatinine), and 4.6 µg/g creatinine (range, < 0.25–18.4 µg/g creatinine) from the first void, pre-, and post-shift samples, respectively.

[Sivulka & Seilkop \(2009\)](#) reconstructed historical exposures to nickel oxide and metallic nickel in the US nickel alloy industry from personal and area measurements collected at 45 plants since the 1940s ($n = 6986$ measurements). Of the measurements included in the database, 96% were personal breathing zone samples, and 4% were stationary area samples. The data provided evidence of a strongly decreasing gradient of airborne total nickel levels from the 1940s to the present.

1.5.3 Dietary exposure

Nickel has been measured in a variety of foodstuffs as “total nickel.” Average concentrations are in the range of 0.01–0.1 mg/kg, but can be as high as 8–12 mg/kg in certain foods ([EVM, 2002](#); [WHO, 2007](#)). Factors influencing the concentration of nickel in food include the type of food (e.g. grains, vegetables, fruits versus seafood, mother’s milk versus cow’s milk), growing conditions (i.e. higher concentrations have been observed in food grown in areas of high environmental or soil contamination), and food preparation techniques (e.g. nickel content of cooking utensils, although the evidence for leaching from stainless steel cookware is somewhat mixed) ([EVM, 2002](#); [WHO, 2007](#)).

The highest mean concentrations of nickel have been measured in beans, seeds, nuts and grains (e.g. cocoa beans, 9.8 µg/g; soyabeans, 5.2 µg/g; soya products, 5.1 µg/g; walnuts, 3.6 µg/g; peanuts, 2.8 µg/g; oats, 2.3 µg/g; buckwheat, 2.0 µg/g; and oatmeal, 1.8 µg/g). Although nickel concentrations vary by type of foodstuff, average levels are generally within the range of 0.01–0.1 µg/g. Reported ranges for some common food categories are: grains, vegetables and fruits, 0.02–2.7 µg/g; meats, 0.06–0.4 µg/g; seafood, 0.02–20 µg/g; and dairy, < 100 µg/L (EVM, 2002). This variability in nickel content makes it difficult to estimate the average daily dietary intake of nickel (EVM, 2002).

1.5.4 Biomarkers of exposure

Biomarker levels are influenced by the chemical and physical properties of the nickel compound studied, and by the time of sampling. It should be noted that the nickel compounds, the timing of collection of biological samples (normally at the end of a shift), and the analytical methods used differ from study to study, and elevated levels of nickel in biological fluids and tissue samples are mentioned only as indications of uptake of nickel, and may not correlate directly to exposure levels (IARC, 1990).

Atomic absorption spectrometry (AAS) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are the most common analytical methods used to determine “total nickel” concentrations in biological materials (such as blood, tissues, urine, and faeces). Nickel content can also be measured in other tissues, such as nails and hair, although specific procedures for dissolving the sample must be followed (ATSDR, 2005). The presence of calcium, sodium or potassium interferes with the quantification of nickel in biological samples, and specific techniques (e.g. isotope dilution) must be used to validate nickel measurements (ATSDR, 2005). Serum and urine samples are the most useful

biomarkers of recent exposure, reflecting the amount of nickel absorbed in the previous 24–48 hours (NTP, 2000).

Minoia *et al.* (1990) used atomic absorption spectroscopy and neutron activation analysis to determine trace element concentrations of nickel in urine, blood, and serum collected from non-exposed healthy subjects ($n = 1237$; 635 males, 602 females) from the Lombardy region of northern Italy. The mean nickel level in urine samples ($n = 878$) was 0.9 µg/L (range, 0.1–3.9 µg/L); in blood samples ($n = 36$), 2.3 µg/L (range, 0.6–3.8 µg/L); and in serum samples ($n = 385$), 1.2 µg/L (range, 0.24–3.7 µg/L).

In a Norwegian-Russian population-based health study, human nickel exposure was investigated in the adult population living near a nickel refinery on both sides of the Norwegian-Russian border during 1994–95. Urine samples were collected from inhabitants, aged 18–69 years, of Nikel, Zapolyarny, and Sor-Varanger and also from individuals living more remotely from the Kola Peninsula nickel-producing centres (in the Russian cities of Apatity and Uмба, and the Norwegian city of Tromsø). A total of 2233 urine specimens were collected and analysed for nickel using electrothermal atomic absorption spectrometry. The highest urinary nickel concentrations were observed in residents of Nikel (median, 3.4 µg/L; mean, 4.9 µg/L; range, 0.3–61.9 µg/L), followed by Uмба (median, 2.7 µg/L; mean, 4.0 µg/L; range, 1.0–17.0 µg/L), Zapolyarny (median, 2.0 µg/L; mean, 2.8 µg/L; range, 0.3–24.2 µg/L), Apatity (median, 1.9 µg/L; mean, 2.6 µg/L; range, 0.3–17.0 µg/L), Tromsø (median, 1.2 µg/L; mean, 1.4 µg/L; range, 0.3–6.0 µg/L), and Sor-Varanger (median, 0.6 µg/L; mean, 0.9 µg/L; range, 0.3–11.0 g/L). The Russian participants all had a higher urinary nickel average than those from Norway, regardless of geographic location (Smith-Sivertsen *et al.*, 1998).

Ohashi *et al.* (2006) determined reference values for nickel in urine among women of the general population of 11 prefectures in Japan.

A total of approximately 13000 urine samples were collected in 2000–05 from 1000 adult women aged 20–81 years who had no occupational exposure to nickel. Nickel in urine was analysed by graphite furnace atomic absorption spectrometry. The observed geometric mean concentration for nickel was 2.1 µg/L (range, < 0.2–57 µg/L). After correction for creatinine, the geometric mean concentration was reported as 1.8 µg/L (maximum, 144 µg/L).

1.5.5 Other sources of exposure

Nickel, chromium, and cobalt are common causes of allergic contact dermatitis. In the early 1990s it was recommended that household and other consumer products should not contain more than 5 ppm of each of nickel, chromium, or cobalt, and that, for an even greater degree of protection, the ultimate target level should be 1 ppm. In a recent survey, selected consumer products had the following nickel levels (ppm): hand-wash powders, 0.9; heavy duty powders, 0.5; laundry tablets, 0.5; liquid/powder cleaners, 0.4; heavy duty liquids, 0.1; machine/hand-wash liquids, 0.1; hand-wash liquids, 0.1, fine wash liquids, 0.1; and dishwashing liquids, 0.1 ([Basketter et al., 2003](#)).

Potential iatrogenic sources of exposure to nickel are dialysis treatment, leaching of nickel from nickel-containing alloys used as prostheses and implants, and contaminated intravenous medications ([Sunderman, 1984](#)).

2. Cancer in Humans

The previous *IARC Monograph* was based upon evidence of elevated risk of lung and nasal cancers observed among workers involved in a variety of nickel sulfide ore smelting and nickel refining processes that included high-temperature processing of nickel matte, nickel–copper matte, electrolytic refining, and Mond process

refining. The exposures included metallic nickel, nickel oxides, nickel subsulfide, soluble nickel compounds, and nickel carbonyl. These cohort studies were conducted mainly in Canada, Norway, Finland, and in the United Kingdom ([IARC, 1990](#); [ICNCM, 1990](#)).

2.1 Cohort studies and nested case–control studies

Since the previous *IARC Monograph*, several studies have extended follow-up to some of the previous cohorts, and have provided additional cohort and nested case–control analyses related mostly to lung cancer risk, and taking into account potential confounding factors as well as mixed exposures to water-soluble and -insoluble nickel compounds. Among the most common occupations with exposure to nickel compounds are stainless steel welders, who are also exposed to chromium (VI) compounds, and other compounds. Although there have been some cohort studies of stainless steel welders, these are not recorded in the present *Monograph* because it is difficult to ascribe any excess risks in these cohorts to nickel compounds specifically. Key results of some of these cohort studies can be found in Table 2.1 of the *Monograph* on chromium (VI) in this volume.

Also, since the previous *IARC Monograph*, experimental evidence has become available that nickel metal dust can become solubilized and bioavailable after inhalation. Consequently, separately classifying nickel and nickel compounds was viewed by the Working Group as not warranted. A similar distinction has not been made for other metals, e.g. beryllium and cadmium, in other *IARC Monographs*. Accordingly, this review did not exclude studies that focused on metallic nickel, unless they, for other reasons, were considered uninformative.

2.1.1 Cancer of the lung

Studies were carried out in nickel smelters and refineries in Canada, Norway (Kristiansand), Finland, and the United Kingdom (Clydach). Because the refining processes differed in the plants, the exposure profiles to various nickel compounds were different across the cohorts. Nonetheless, increased risks for lung cancer were found in cohorts from all of these facilities (see Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.1.pdf>).

High risks for lung cancers were observed among calcining workers in Canada, who were heavily exposed to both sulfidic and oxidic nickel (nickel sulfides and oxides). A high lung cancer rate was also seen among nickel plant cleaners in Clydach who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides could not be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in Clydach calcining furnaces and nickel plant cleaners, exposed to high levels of metallic nickel, had high lung cancer risks (see Table 2.1 online). A substantial excess risk for lung cancer among hydrometallurgy workers in Norway was mainly attributed to their exposure to water-soluble nickel. Their estimated exposures to other types of nickel (metallic, sulfidic, and oxidic) were as much as an order of magnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. High risks for lung cancer were also observed among electrolysis workers at Kristiansand (Norway). These workers were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate and nickel chloride (after 1953) were the only or predominant soluble nickel species present in these areas.

An update of the Kristiansand cohort by [Andersen *et al.* \(1996\)](#) demonstrated a dose-response relationship between cumulative exposure to water-soluble nickel compounds and lung cancer ($P < 0.001$) when adjustment was made for age, smoking, and nickel oxide. The risk was increased 3-fold in the highest soluble nickel dose group. A lesser, but positive, effect was seen between cumulative exposure to nickel oxide and risk of lung cancer, also with adjustment for age, cigarette smoking, and exposure to water-soluble nickel (P for trend = 0.05, see [Table 2.2](#)).

Subsequent to the [Andersen *et al.* \(1996\)](#) study, an industrial hygiene study re-evaluated exposure among the Norwegian refinery workers based on new information related to nickel species and exposure levels ([Grimsrud *et al.*, 2000](#)). [Grimsrud *et al.* \(2003\)](#) updated the lung cancer incidence among the Norwegian nickel refinery workers (see Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.3.pdf>). The strongest gradient for cumulative exposure and lung cancer was found in relation to water-soluble nickel adjusted for cigarette-smoking habits, which was known for 4728 (89%) of the cohort members. Regarding species of water-soluble nickel compounds, the risk from potential exposure to nickel chloride was similar to that for nickel sulfate. The nickel electrolysis process (using nickel sulfate) changed to a nickel-chloride-based process in 1953, and workers hired in 1953 or later had a similar lung cancer risk (standardized incidence ratio [SIR], 4.4; 95%CI: 1.8–9.1) as for those employed in the same area before 1953 when the nickel sulfate was used (SIR, 5.5; 95%CI: 3.0–9.2). Analyses by year of first employment indicated that those initially employed after 1978 continued to demonstrate a significantly elevated risk of lung cancer (SIR, 3.7; 95%CI: 1.2–8.7), suggesting continued exposure to nickel compounds.

[Grimsrud *et al.* \(2002\)](#) conducted a case-control study of lung cancer nested within the

Nickel and nickel compounds

Table 2.2 Relative risks of lung cancer by cumulative exposure to soluble nickel and nickel oxide, considering the two variables simultaneously by multivariate Poisson regression analysis^a

Variable	Mean exposure (mg/m ³)	Cases	Relative risk	95%CI	Test for linear trend
Soluble nickel					$P < 0.001$
< 1	0.1	86	1.0	Referent	
1–4	2.3	36	1.2	0.8–1.9	
5–14	8.8	23	1.6	1.0–2.8	
≥ 15	28.9	55	3.1	2.1–4.8	
Nickel oxide					$P = 0.05$
< 1	0.4	53	1.0	Referent	
1–4	2.5	49	1.0	0.6–1.5	
5–14	8.3	53	1.6	1.0–2.5	
≥ 15	44.3	45	1.5	1.0–2.2	

^a Workers with unknown smoking habits were excluded (three cases of lung cancer).

Adjusted for smoking habits and age.

From [Andersen et al. \(1996\)](#)

cohort of Norwegian nickel refinery workers (see Table 2.3 online). Exposure groups were determined based on quintiles of the exposure variables in the controls. Analyses by cumulative exposure adjusted for cigarette smoking indicated that odds ratios for lung cancer in the highest cumulative exposure category of water-soluble nickel, sulfidic nickel, metallic nickel, and oxidic nickel were 3.8 (95%CI: 1.6–9.0), 2.8 (95%CI: 1.1–6.7), 2.4 (95%CI: 1.1–5.3), and 2.2 (95%CI: 0.9–5.4), respectively. The trend for cumulative exposure and lung cancer was significant for water-soluble nickel compounds only ($P = 0.002$). There was, however, a high degree of correlation with exposure to nickel and nickel compounds as a whole, making evaluation of the independent effect of individual compounds difficult. Nonetheless, when data were further adjusted for exposure to water-soluble compounds, there were no significant trends in the odds ratios by cumulative exposure to sulfidic, oxidic, or metallic nickel. The odds ratios related to the highest cumulative exposure group for each of these compounds were 1.2 (95%CI: 0.5–3.3), 0.9 (95%CI: 0.4–2.5), and 0.9 (95%CI: 0.3–2.4), respectively (see [Table 2.4](#)). In further analyses, with adjustment for cigarette smoking, arsenic, asbestos, sulfuric

acid mist, cobalt and occupational carcinogenic exposures outside the refinery, the strong association between lung cancer and water-soluble nickel remained ([Grimsrud et al., 2005](#)).

[Anttila et al. \(1998\)](#) updated an earlier cohort study of Finnish nickel refinery and copper/nickel smelter workers ([Karjalainen et al., 1992](#)). Among refinery workers employed after 1945, who were exposed primarily to nickel sulfate, an excess of lung cancer was observed in the overall cohort (SIR, 2.61; 95%CI: 0.96–5.67), and the lung cancer risk increased with > 20 years of latency (SIR, 3.38; 95%CI: 1.24–7.36, based on six cases). Among smelter workers, lung cancer was also elevated in the overall cohort (SIR, 1.39; 95%CI: 0.78–2.28), and, similarly, a significant increase in lung cancer risk with > 20 years of latency was observed (SIR, 2.00; 95%CI: 1.07–3.42).

There have been three subsequent reports that provide additional information on refinery workers in Wales (the United Kingdom) exposed to nickel carbonyl and other nickel compounds.

[Easton et al. \(1992\)](#) carried out an updated analysis of Welsh nickel refinery workers to determine which nickel compounds were responsible for lung cancer among the 2524 workers employed

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Table 2.4 Adjusted^a odds ratios for lung cancer by exposure to sulfidic, oxidic or metallic nickel in a nested case–control study of Norwegian nickel refinery workers observed during 1952–95

Cumulative exposure to nickel ^b	Odds ratio	95% CI
Sulfidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.9
Low-medium	2.2	0.9–5.5
Medium	1.8	0.7–4.5
Medium-high	1.3	0.5–3.3
High	1.2	0.5–3.3
Likelihood ratio test: $P = 0.344$		
Oxidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.8
Low-medium	1.8	0.7–4.5
Medium	1.4	0.6–3.7
Medium-high	1.5	0.6–3.7
High	0.9	0.4–2.5
Likelihood ratio test: $P = 0.406$		
Metallic nickel		
Unexposed	1.0	
Low	1.2	0.5–2.9
Low-medium	1.0	0.5–2.4
Medium	1.0	0.4–2.3
Medium-high	1.0	0.4–2.4
High	0.9	0.3–2.4
Likelihood ratio test: $P = 0.972$		

^a Data were adjusted for smoking habits in five categories (never smoker, former smoker, or current smoker of 1–10, 11–20, or > 20 g/day), and for exposure to water-soluble nickel as a continuous variable with natural log-transformed cumulative exposure values ($\ln[(\text{cumulative exposure}) + 1]$).

^b Categories were generated according to quartiles among exposed control. In each of the three analyses, data were unadjusted for the other two insoluble forms of nickel.

From [Grimsrud *et al.* \(2002\)](#)

for > 5 years before the end of 1969, and followed during 1931–85. The model was based on exposures occurring before 1935, and was adjusted for age at first exposure, duration of exposure, and time since first exposure. For lung cancer, the best fitting model suggested risks for soluble and metallic nickel exposures, and much less (if any) risk for nickel oxide or sulfides. [Sorahan & Williams \(2005\)](#) followed during 1958–2000 a group of 812 workers from the cohort of Welsh nickel refinery workers who were hired between 1953–92, and who had achieved > 5 years of employment. The overall lung cancer SMR was

1.39 (95%CI: 0.92–2.01). For those with > 20 years since the start of employment, lung cancer risk was significantly elevated [SMR, 1.65; 95%CI: 1.07–2.41], indicating an elevated risk of lung cancer among those hired since 1953.

[Grimsrud & Peto \(2006\)](#) combined data from the most recent updates of Welsh nickel refinery workers to assess lung cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for lung cancer (SMR, 1.33; 95%CI: 1.03–1.72). [The Working Group noted that

exposures were dramatically reduced during the 1920s.]

[Egedahl et al. \(2001\)](#) updated the mortality data among employees at a hydrometallurgical nickel refinery and fertilizer complex in Fort Saskatchewan, Canada, who had worked for 12 continuous months during 1954–78. Among the 718 men exposed to nickel, the lung cancer SMR was 0.67 (95%CI: 0.24–1.46, based on six deaths). Significant decreases were observed for the ‘all causes of death’ category (SMR, 0.57; 95%CI: 0.43–0.74), and for the ‘all cancer deaths’ category (SMR, 0.47; 95%CI: 0.25–0.81). [The Working Group considered the study uninformative for the evaluation of cancer risks due to a substantial healthy worker effect which may have masked excess mortality that was associated with nickel exposure.]

[Goldberg et al. \(1994\)](#) conducted a 10-year incidence study and a nested case–control study of a cohort of nickel mining (silicate-oxide ores) and refinery workers in New Caledonia, South Pacific. They observed a significant decrease in the incidence of lung cancer, and this was also observed for other respiratory cancers. The results of the case–control study did not show elevated risks for respiratory cancers in relation to low levels of exposure to soluble nickel, nickel sulfide, or metallic nickel. For all three nickel exposures separately, the odds ratios were 0.7.

[The Working Group noted that in most of these studies of lung cancer risk in smelters and refineries, there was exposure to metallic nickel together with exposure to the other forms of nickel ([Sivulka, 2005](#)). Only one of these studies involved an attempt to evaluate separately the effect of metallic nickel ([Grimsrud et al., 2002](#)).]

Several additional studies of workers with potential exposure to metallic nickel were reviewed by the Working Group. [Arenia et al. \(1998\)](#) evaluated mortality among workers exposed to “high nickel alloys” in the USA. A recent industrial hygiene analysis indicated that oxidic nickel comprised 85% of the total nickel

exposure of these workers, with the rest being mostly metallic nickel ([Sivulka & Seilkop, 2009](#)). Compared to US national rates, lung cancer was significantly elevated among white men (SMR, 1.13; 95%CI: 1.05–1.21), among non-white men the SMR was 1.08 (95%CI: 0.85–1.34), and in women 1.33 (95%CI: 0.98–1.78). [The Working Group noted that the lung cancer SMR for the entire cohort combined was 1.13 (95%CI: 1.06–1.21) based on 955 observed deaths.] The authors also calculated SMRs based on local (SMSA) rates for the separate population subgroups. When calculated for the total cohort, the resulting SMR was [1.01; 95%CI: 0.95–1.08]. [The Working Group noted that it is difficult to interpret the use of local rates when the study population was derived from 13 separate areas located throughout the USA, but the use of rates from urban areas could have overestimated the expected number of deaths from lung cancer. The Working Group noted that the overall SMR for lung cancer in this study compared with the national population was statistically significant, and provides some evidence of an association between exposures in these plants and lung cancer. It appears that the primary exposure was to nickel oxide and thus, the study cannot be used to evaluate the specific carcinogenicity of metallic nickel. Analysis of lung cancer by duration of employment did not indicate a dose–response. The Working Group noted that duration of employment is a poor measure of exposure when exposures are known to have declined over time.]

There have also been a series of studies conducted in the French stainless steel industry that involved co-exposure to several known and potential human lung carcinogens, and the most detailed exposure assessment considered nickel and chromium combined ([Moulin et al. 1990, 1993a, b, 1995, 2000](#)).]

The only cohort of workers exposed to metallic nickel in the absence of other nickel compounds (Oak Ridge cohort) included only 814 workers, and provided little statistical power to evaluate

lung cancer risk ([Godbold & Tompkins, 1979](#); [Cragle et al., 1984](#)).

[Sorahan \(2004\)](#) updated the mortality rate among employees manufacturing nickel alloys at the plant in Hereford, the United Kingdom. The study showed a significant decrease for ‘all causes of death’ (SMR, 0.79), for ‘all cancer deaths’ (SMR, 0.81), and a non-significant decrease for lung cancer (SMR, 0.87; 95%CI: 0.67–1.11).

[Pang et al. \(1996\)](#) evaluated cancer risks among 284 men who were employed for at least 3 months during 1945–75 in a nickel-plating department, and followed through 1993. For lung cancer, the overall SMR was 1.08 (95%CI: 0.54–1.94). For those with > 20 years latency, eight lung cancer deaths were observed versus 6.31 expected [SMR, 1.27; 95%CI: 0.55–2.50].

Several other studies reviewed by [Sivulka \(2005\)](#) had mixed exposure to metallic nickel and other nickel compounds, and provide no evidence on the carcinogenicity of metallic nickel alone. Furthermore, many of the studies cited in the review involved mixed exposures in stainless steel welding and grinding, and manufacturing nickel alloys ([Cox et al., 1981](#); [Enterline & Marsh, 1982](#); references from Tables 5 and 6 of [Sivulka, 2005](#)), and therefore were not considered relevant for evaluating the carcinogenicity of nickel and/or nickel compounds.

2.1.2 Cancer of the nasal cavity

Increased risks for nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand), and the United Kingdom (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant), and extraction of nickel salts from concentrated solution (hydrometallurgy) in the United Kingdom (see Table 2.5 available

at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.5.pdf>).

In the Norwegian study, [Andersen et al. \(1996\)](#) demonstrated a dose–response relationship between both cumulative exposure to water-soluble nickel and nickel oxide compounds and the risk of nasal cancer. The SIR (compared to the general population) was the highest in the group of workers with the highest cumulative exposure to soluble nickel compounds combined with insoluble nickel compounds (SIR, 81.7; 95%CI: 45–135; based on 15 cases). For workers with the highest cumulative exposure to nickel oxide, the SIR was 36.6 (95%CI: 19.5–62.5; based on 13 cases) (see Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.6.pdf>).

An update of nasal cancer in Finnish refinery workers after 20 years since the first exposure to nickel reported an SIR of 67.1 (95%CI: 12–242.0; based on two cases) ([Anttila et al., 1998](#)). An additional nasal cancer was observed 2 years after the follow-up period ended, and a fourth potential nasal cancer (classified as a nasopharyngeal cancer, 0.04 expected) was reported during the follow-up period. No nasal cancers were observed among the smelter workers who were exposed primarily to nickel matte, nickel subsulfide, nickel sulfides, and other metals.

[Easton et al. \(1992\)](#) attempted to identify the nickel compounds responsible for nasal cancer among 2524 Welsh nickel refinery workers employed for > 5 years before the end of 1969, and followed during 1931–85. As shown in [Table 2.7](#), the risk for nasal cancer was in the range of 73–376 times the expected for those first employed before 1930, based on 67 nasal cancer deaths. A statistical model that fitted to the data on men whose exposures occurred before 1935, and that adjusted for age at first exposure, duration of exposure, and time since first exposure indicated that the soluble nickel effect on nasal cancer risk is the only one significant.

Table 2.7 Observed and expected deaths from nasal sinus cancer (1931–85) by year of first employment

Year first employed	Observed deaths	Expected deaths	SMR	95% CI
< 1920	55	0.15	376	276–477
1920–29	12	0.17	73	36–123
1930–39	1	0.07	14	0.4–80
1940–49	0	0.06	–	–
> 1950	0	0.06	–	–
Total	68	0.45	151	117–192

From [Easton et al. \(1992\)](#)

[Grimsrud & Peto \(2006\)](#) combined data from the most recent updates of Welsh nickel refinery workers to assess nasal cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for nasal cancer (SMR, 8.70; 95%CI: 1.05–31.41, based on two observed deaths).

In one study of Swedish Ni–Cd battery workers, three nasal cancer cases versus 0.36 expected were observed (SIR, 8.32; 95%CI: 1.72–24.30) ([Järup et al., 1998](#)). Two of these cases occurred among workers exposed to greater than 2 mg/m³ nickel (SIR, 10.8; 95%CI: 1.31–39.0).

2.1.3 Other cancer sites

Other than for lung cancer and nasal sinus cancer, there is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at other sites.

The results of several studies of workers exposed to nickel compounds showed a statistically elevated risk of a site-specific cancer in addition to lung and nasal cancer. A study of sinter plant workers in Canada showed a significantly elevated risk of cancer of the buccal cavity and pharynx ([IARC, 1990](#)). In a study in the Norwegian nickel-refining industry, a significant excess of laryngeal cancer was observed among roasting and smelter workers ([Magnus et al., 1982](#)).

Stomach cancer was significantly elevated among men employed in a nickel- and

chromium-plating factory in the United Kingdom ([Burgess, 1980](#)). A study of men employed in a nickel-plating department ([Pang et al., 1996](#)) showed a significant elevation in stomach cancer. Another study ([Anttila et al., 1998](#)) demonstrated a significant excess of stomach cancer among nickel refinery workers.

A study of workers producing alloys with a high nickel content ([Arena et al., 1998](#)) demonstrated a significant excess of colon cancer among ‘non-white males’ (relative risk, 1.92; 95%CI: 1.28–2.76), and a 2-fold risk of kidney cancer among white males employed in ‘melting.’ However, the excess risk was not associated with length of employment or time since first employment. [The Working Group noted that specific data was not provided in the article.]

A meta-analysis ([Ojajärvi et al., 2000](#)) reported a significantly elevated risk for pancreatic cancer that upon further evaluation actually indicated no elevation in risk ([Seilkop, 2002](#)).

A population-based case-control study ([Horn-Ross et al., 1997](#)) based on self-reported occupational exposure, showed a dose-response relationship between cumulative exposure to nickel compounds/alloys and salivary gland cancer. [The Working Group noted that the author corrected the direction of signs in Table 2 of her report in a subsequent erratum.]

2.2 Synthesis

The Working Group evaluated a large body of evidence and concluded that there is an elevated risk of lung and nasal sinus cancer among nickel refinery workers ([IARC, 1990](#); [Andersen et al., 1996](#); [Anttila et al., 1998](#); [Grimsrud & Peto, 2006](#)), and an elevation in lung cancer risk among nickel smelter workers ([IARC, 1990](#); [Anttila et al., 1998](#)).

Epidemiological studies have provided evidence for lung cancer related to specific nickel compounds or classes of compounds (based, for example, on water solubility). Evidence for elevated risk of lung cancer in humans was demonstrated specifically for nickel chloride ([Grimsrud et al., 2003](#)), nickel sulfate, water-soluble nickel compounds in general ([Andersen et al., 1996](#); [Grimsrud et al., 2002, 2003](#); [Grimsrud et al., 2005](#)), insoluble nickel compounds, nickel oxides ([Andersen et al., 1996](#); [Anttila et al., 1998](#); [Grimsrud et al., 2003](#)), nickel sulfides ([Grimsrud et al., 2002](#)), and mostly insoluble nickel compounds ([Andersen et al., 1996](#)).

A study that modelled risks of various nickel compounds and lung cancer risk identified both water-soluble nickel and metallic nickel as contributing to risk ([Easton et al., 1992](#)). The largest study addressing worker exposure to metallic nickel (in combination with nickel oxide) showed a small but significant elevation in lung cancer risk ([Arena et al., 1998](#)).

Other studies specifically addressing nickel metal exposures were uninformative and did not allow any judgment as to whether such exposures should be considered different with regard to cancer risk. It was not possible to entirely separate various nickel compounds in dose–response analyses for specific nickel compounds. In one analysis, an additional adjustment for water-soluble nickel compounds on risk of lung cancer indicated little association with cumulative exposure to sulfidic, oxidic or metallic nickel. One study of Ni–Cd battery workers exposed to nickel hydroxide and cadmium oxide demonstrated a

significant risk of cancer of the nose and nasal sinuses.

On the basis of the Norwegian studies of refinery workers, the evidence is strongest for water-soluble nickel compounds and risk for lung cancer. The confidence of the Working Group in the above findings was reinforced by the availability of information on cigarette smoking for 89% of the Norwegian cohort, and the adjustments made for potential confounding exposures.

3. Cancer in Experimental Animals

Nickel and nickel compounds have been tested for carcinogenicity by intramuscular injection to rats, mice, and rabbits; by repository injections at multiple sites in hamsters, rabbits and mice; by intraperitoneal administration to rats and mice; and by intratracheal instillation, intrapleural, intrarenal, intraocular, inhalation, and subcutaneous exposure to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* ([IARC, 1990](#)) were reconsidered in this evaluation, and summarized in the text.

3.1 Oral administration

3.1.1 Nickel sulfide

In a 2-year multiple dose study, oral nickel sulfate hexahydrate given to male and female rats did not result in carcinogenesis ([Heim et al., 2007](#)).

3.1.2 Nickel chloride

Nickel chloride was tested for carcinogenicity by oral administration in female hairless mice (CRL: SK1-hrBR). Mice were exposed to ultra-violet radiation (UVR) alone, nickel chloride alone (given in the drinking-water) and UVR + various concentrations of nickel chloride. Nickel

Table 3.1 Studies of cancer in experimental animals exposed to nickel compounds (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 104 wk Heim et al. (2007)	Nickel sulfate hexahydrate 0, 10, 30, 50 mg/kg/d (gavage), ^a 60/group/sex	Keratoacanthoma (tail): M–low dose 15% (numbers not provided)	$P < 0.001$	Age at start, 6 wk 99.9% pure Exposure-related decreased bw in males and females (2 highest dose groups) Exposure-related increased mortality ($P_{\text{trend}} < 0.008$) in high dose females but not males
Mouse, CRL: Sk1- hrBR (F) 224 d Uddin et al. (2007)	Nickel chloride in drinking- water at 3 wk of age 3 wk later UV treatment (1.0 kJ/m ²) 3 d/wk for 26 wk Groups, number of animals Group 1: Controls, 5 Group 2: UV only, 10 Group 3: 500 ppm, 10 Group 4: UV + 20 ppm, 10 Group 5: UV + 100 ppm, 10 Group 6: UV + 500 ppm, 10 5–10/group	Skin (tumours): Number of tumours/ mice at 29 wk Group 1: 0 Group 2: 1.7 ± 0.4 Group 3: 0 Group 4: 2.8 ± 0.9 Group 5: 5.6 ± 0.7 Group 6: 4.2 ± 1.0	Group 5 vs Group 2 $P < 0.05$ Group 6 vs Group 2 $P < 0.05$	Age at start, 3 wk Nickel had no effect on growth of the mice Nickel levels in skin increased with dose

^a vehicle not stated

d, day or days; F, female; M, male; UVR, ultraviolet radiation; vs, versus; wk, week or weeks

chloride alone did not cause skin tumours by itself, but when combined with UVR, it increased the UVR-induced skin tumour incidence ([Uddin et al., 2007](#)).

See [Table 3.1](#).

3.2 Inhalation exposure

3.2.1 Nickel sulfate hexahydrate

Nickel sulfate hexahydrate was not shown to be carcinogenic in male or female rats or male or female mice when given by inhalation in a 2-year bioassay study ([Dunnick et al., 1995](#); [NTP, 1996a](#)). Analysis of lung burden showed that nickel was cleared from the lungs ([Dunnick et al., 1995](#)).

3.2.2 Nickel subsulfide

Nickel subsulfide induced lung tumours in rats exposed by inhalation ([Ottolenghi et al., 1975](#)).

Inhalation of nickel subsulfide increased the incidence of aveolar/bronchiolar adenomas and carcinomas in male F344 rats, and increased combined lung tumours in females ([Dunnick et al., 1995](#); [NTP, 1996b](#)). Nickel subsulfide also increased the incidence of adrenal pheochromocytomas (benign or malignant) in male and female rats, malignant pheochromocytomas were increased in male rats. Significant dose-related trends were observed for both lung and adrenal tumours in both sexes.

3.2.3 Nickel oxide

The carcinogenicity of nickel oxide was investigated in 2-year inhalation studies in F344 male and female rats, and B6C3F₁ male and female mice. Nickel oxide induced tumours of the lung (alveolar bronchiolar adenomas or carcinomas), and adrenal medulla (malignant and benign pheochromocytoma) in both sexes of rats. Nickel oxide also increased the incidence of lung tumours in low-dose females but not in male mice ([NTP, 1996c](#)).

3.2.4 Metallic nickel

Inhaled metallic nickel increased the incidence of adrenal pheochromocytomas (benign, malignant, and benign and malignant combined) in male rats and adrenal cortex tumours in female rats ([Oller et al., 2008](#)). Dose-related responses were observed for both types of adrenal tumours. No significant increases in lung tumours occurred. Elevated blood levels of nickel indicated that metallic nickel was bioavailable systematically after inhalation ([Oller et al., 2008](#)).

3.2.5 Other forms of nickel

Nickel carbonyl induced lung carcinomas after inhalation exposure ([Sunderman et al., 1957, 1959](#)).

See [Table 3.2](#).

3.3 Parenteral administration

3.3.1 Nickel subsulfide

(a) Mouse

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in mice ([IARC, 1990](#)).

No increase in lung tumour incidence was observed in male strain A/J mice, 20 or 45 weeks after exposure to various treatment regimens

of nickel subsulfide ([McNeill et al., 1990](#)). In another study, nickel subsulfide induced injection-site tumours in all three strains of mice, with the order of susceptibility to tumour formation being C3H, B6C3F₁, and C57BL6 ([Rodriguez et al., 1996](#)). [Waalkes et al. \(2004, 2005\)](#) studied the carcinogenic response to nickel subsulfide in MT-transgenic and MT-null mice. Intramuscular administration of nickel subsulfide increased the incidence of injection-site tumours (primarily fibrosarcoma) in MT-transgenic and concordant wild-type mice, and lung tumours in MT-transgenic mice ([Waalkes et al., 2004](#)). In MT-null mice and concordant wild-type mice, intramuscular injection of nickel sulfide induced fibrosarcomas as well ([Waalkes et al., 2005](#)). MT-expression, either overexpression (MT-transgenic mice) or no expression (MT-null), did not significantly affect the carcinogenic response to nickel.

(b) Rat

Nickel subsulfide induced lung tumours in rats exposed by intratracheal instillation ([Pott et al., 1987](#)). Intrarenal injection resulted in dose-related increases in renal cell tumours, and intraocular injection resulted in eye tumours in rats ([Jasmin & Riopelle, 1976](#); [Sunderman et al., 1979](#); [Albert et al., 1982](#); [Sunderman, 1983](#)). Implantation of nickel subsulfide pellets into rat heterotrophic tracheal transplant caused carcinomas and sarcomas ([Yarita & Nettesheim, 1978](#)). Local tumours were also observed in rats tested by intramuscular and intrarenal injection with nickel disulfide or nickel monosulfide (crystalline but not amorphous form), and in rats tested by intramuscular injection with nickel ferrosulfide matte ([Sunderman, 1984](#); [Sunderman et al., 1984](#)).

When administered by intrarenal injection to F344 male rats, nickel subsulfide induced renal sarcomas ([Kasprzak et al., 1994](#)), which showed metastases to the lung, liver, and spleen. Injection site tumours (rhabdomyosarcoma,

Table 3.2 Studies of cancer in experimental animals exposed to nickel compounds or nickel powder (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel sulfate hexahydrate				
Rat, F344 (M, F) 104 wk Dunnick et al. (1995), NTP (1996a)	0, 0.125, 0.25, 0.5 mg/m ³ (equivalent to 0, 0.03, 0.06, 0.11 mg nickel/m ³) for 6 h/d, 5 d/wk 63–65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–2 ^a /54, 0/53, 1/53, 3/53 F ^b –0/52, 0/53, 0/53, 1/54 Adrenal medulla (pheochromocytomas, benign or malignant): M–16/54, 19/53, 13/53, 12/53 F–2/52, 4/52, 3/52, 3/54		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Mean bw of high-dose females were slightly lower than controls. Nickel lung burden values increased with increasing exposure (at 15 mo, 0.15–1.7 µg Ni/g lung)
Mouse, B6C3F ₁ (M, F) 104 wk Dunnick et al. (1995), NTP (1996a)	0, 0.25, 0.5, 1.0 mg/m ³ (equivalent to 0, 0.06, 0.11, 0.22 mg nickel/m ³) 6 h/d, 5 d/wk 63–65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas): M–13/61, 18/61, 7/62, 8/61 F–7/61, 6/60, 10/60, 2/60		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Bw of high-dose males and all exposed female groups were decreased Nickel lung burden (µg Ni/g lung) below limit of detection at 7 and 15 mo interim evaluations

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Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Rat, F344 (M, F) 104 wk Dunnick et al. (1995), NTP (1996b)	0, 0.15, 1 mg/m ³ (equivalent to 0, 0.11, 0.73 mg nickel/m ³) 6 h/d, 5 d/wk 63/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–0/53, 6/53, 11/53 F–2/53, ^a 6/53, 9/53 Adrenal medulla (pheochromocytomas, benign or malignant): M–14/53, 30/53, 42/53 F–3/53, 7/53, 36/53	M: mid dose $P < 0.05$, high dose $P \leq 0.01$, $P_{\text{trend}} < 0.01$ F: mid dose $P \leq 0.05$ vs historical control, high dose $P < 0.05$, $P_{\text{trend}} < 0.05$ M: mid dose $P < 0.01$, high dose < 0.001 , $P_{\text{trend}} < 0.001$ F: high dose, $P < 0.001$ $P_{\text{trend}} < 0.001$	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Bw in high-dose groups Nickel lung burden increased with increasing exposure but reached steady-state by 15 mo (4–7 µg Ni/g lung). Lung carcinomas also were significantly increased in high-dose males
Mouse, B6C3F ₁ (M, F) 104 wk Dunnick et al. (1995), NTP 1996b	0, 0.6, 1.2 mg/m ³ (equivalent to 0, 0.44, 0.9 mg nickel/m ³) 6 h/d, 5 d/wk 63/group	Lung (alveolar/bronchiolar adenomas or carcinomas): M–13/61, 5/59, 6/58 F–9/58, 2/59, 3/60	$P = 0.038N^h$ mid dose vs control $P = 0.028N^h$ mid dose vs control $P = 0.050N^h$ high dose vs control	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Mean bw lower in exposed groups than control group. Nickel lung burden increased with exposure concentration and with time (at 15 mo, 12–26 µg Ni/g lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 78–80 wk + held 30 wk Ottolenghi et al. (1975)	Nickel subsulfide with or without 1 mo pre-exposure to the airborne system (clean air or nickel sulfide dust 0.97 ± 0.18 mg/m ³ for 5 d/wk), followed by injection of hexachlorotetrafluorobutane to half the animals, thereafter the inhalation exposure was continued for all animals 16 exposure groups (8 groups/sex)	Lung (adenomas, adenocarcinomas, squamous cell carcinomas, fibrosarcomas): NiS-17 (M), 12 (F) Controls-1 (M), 1 (F) Adrenal gland (hyperplasias and pheochromocytomas): NiS-12% Controls-1.1%	M, F; $P < 0.01$ $P < 0.01$	Pre-exposure: animals assigned airborne system for 1 mo No pre-exposure: animals housed in normal conditions for 1 mo Inj. = intravenous injection with pulmonary infraction agent Treatment-related decreased survival and decreased bw in males and females starting at 26 wk Inflammatory response – pneumonitis, bronchitis and emphysema Hyperplasias and squamous metaplastic changes in bronchial and bronchiolo-alveolar regions Infraction had no effect on carcinogenicity
	<u>Pre-exposure</u> Inj. Controls: 29 (M), 28 (F) Inj. NiS: 29 (M), 28 (F) No Inj. Controls: 28 (M), 30 (F) No Inj. NiS: 22 (M), 26 (F) No Pre-exposure Inj. Controls: 32 (M), 32 (F) Inj. NiS: 24 (M), 32 (F) No Inj. Controls: 31 (M), 31 (F) No Inj. NiS: 32 (M), 26 (F)			

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Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M, F) 104 wk Dunnick et al. (1995) , NTP (1996c)	0, 0.62, 1.25, 2.5 mg/m ³ (equivalent to 0, 0.5, 1.0, 2.0 mg nickel/ m ³) 6 h/d, 5 d/wk 65/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas, or squamous cell carcinomas): M–1 ⁹ /54, 1/53, 6/53, 4/52 F–1/53, 0/53 ^d , 6/53, 5/54 Adrenal medulla (pheochromocytomas, benign or malignant): M–27/54, 24/53, 27/53, 35/54 F– 4/51, 7/52, 6/53, 18/54	M, F: mid dose & high dose, $P \leq 0.05$ vs high dose M: high dose, $P = 0.027$, $P_{\text{trend}} = 0.008$ F: high dose, $P = 0.01$, $P_{\text{trend}} < 0.001$	Age at start, 6 wk 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 262–1116 µg Ni/lung) If the squamous cell carcinomas (lung tumours) are not included, then the mid dose and high dose are significant vs the current controls Significantly increased incidence of malignant pheochromocytomas in high-dose males
Mouse, B6C3F ₁ (M, F) 104 wk Dunnick et al. (1995) , NTP (1996b)	0, 1.25, 2.5, 5.0 mg/m ³ (equivalent to 0, 1.0, 2.0, 3.9 mg nickel/m ³) 6 h/d, 5 d/wk ≈80/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas): M–9/57, 14/67, 15/66, 14/69 F–6/64, 15/66, 12/63, 8/64	F: low dose, $P \leq 0.01$	Age at start, 6 wk; 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 331–2258 µg Ni/lung)

Nickel and nickel compounds

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel metal powder				
Rat, Wistar Crl:Wi (G1XBRL/ Han) (M, F) 12–30 mo Oller et al. (2008)	0, 0.1, 0.4, 1 mg/m ³ for 6 h/d, 5 d/wk, exposure time, additional hold time – Group 1: 0, 24 mo, 6 mo Group 2: 0.1, 24 mo, 6 mo Group 3, F: 0.4, 19 mo, 11 mo Group 3, M: 0.4, 24 mo, 6 mo Group 4, F: 1.0, ~14 mo, 0 mo Group 4, M: 1.0, ~12 mo, 0 mo 50/group	Groups 1, 2, 3 Adrenal gland (pheochromocytomas, benign or malignant): M–0/50, 5/50, 21/50 F–0/50, 5/49, 3/53 Adrenal cortex (adenomas or carcinomas): M–1/50, 3/50, 2/50 F–2/50, 2/49, 7/54	M: 0.4 mg/m ³ Significant increase for benign, malignant, benign combined, significant dose-related response ^f F: 0.4 mg/m ³ Significant increase for combined (adenoma and carcinoma) and significant dose-related response ^f	Age at start, 6 wk 99.9% pure Exposure-related mortality was observed in the high-dose group (Group 4 M, F, these animals were removed from the main study), and in Group 3 F (animals from satellite study reassigned to main study). Exposure-related bw effects were observed in Groups 2 (M), 3 (F &M), and 4 (F &M). Exposure- related lung toxicity was observed. Nickel lung burden (µg Ni/lung) increased with exposure and with time (appeared to reach steady- state at 12 mo) ^g . Increases in adrenal tumours were within published (external) historical controls for Wistar rats

^a Includes 1 squamous cell carcinoma^b Only alveolar bronchiolar adenomas observed in female rats; adjusted rate not reported^c Adjusted rates not provided^d Dunnick reported 1 tumour and NTP technical report reported 0^e Only benign tumours observed.^f P-value not reported calculated by Peto^g Data not available for all time points^h A negative trend or a lower incidence in an exposure group is indicated by N

bw, body weight; d, day or days; h, hour or hours; F, female; M male; mo, month or months; Ni, nickel; NR, not reported; vs, versus; wk, week or weeks

fibromas, malignant fibrous histiocytomas or leiomyosarcomas) were observed in male or female F344 rats administered nickel subsulfide intramuscularly ([Ohmori et al., 1990](#); [Kasprzak & Ward, 1991](#)), and intra-articularly ([Ohmori et al., 1990](#)). One study found that in female rats subjected to bone fractures and treated intramuscularly or intra-articularly had a shorter time to sarcoma formation, reduced survival time, and higher metastatic rate than rats treated with nickel alone ([Ohmori et al., 1990](#)). [Ohmori et al. \(1999\)](#) studied strain susceptibility in male and female Wistar rats, and one strain (CRW) was found to be more sensitive to intramuscular injection of nickel.

(c) *Hamster*

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in hamsters ([IARC, 1990](#)).

(d) *Rabbit*

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies rabbits ([IARC, 1990](#)).

3.3.2 Nickel oxide and hydroxide

Nickel oxide induced lung tumours in rats by intratracheal instillation ([Pott et al., 1987](#)), local sarcomas in mice by intramuscular injection ([Gilman, 1962](#)), and rats by intramuscular, intrapleural, and intraperitoneal injection ([Gilman, 1962](#); [Sunderman & McCully, 1983](#); [Skaug et al., 1985](#); [Pott et al., 1987](#)). Nickel hydroxide induced local sarcomas in rats when tested by intramuscular injection ([Gilman, 1966](#); [Kasprzak et al., 1983](#)).

[Sunderman et al. \(1990\)](#) tested the carcinogenicity of five nickel oxides or nickel-copper oxides in male Fisher 344 rats. The three oxides that induced sarcomas at the injection sites had measurable dissolution rates in body fluids, and were strongly positive in an erythrocytosis

stimulation assay, demonstrating nickel bioavailability.

3.3.3 Nickel acetate

(a) *Mouse*

Nickel acetate when administered by intraperitoneal injection induced lung adenocarcinomas and pulmonary adenomas in Strain A mice ([Stoner et al., 1976](#); [Poirier et al., 1984](#)).

(b) *Rat*

Nickel acetate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats ([Pott et al., 1989, 1990](#)).

A single intraperitoneal injection of nickel acetate initiated renal epithelial tumours (including carcinoma) after promotion using sodium barbital in the drinking-water in male rats ([Kasprzak et al., 1990](#)).

See [Table 3.3](#).

3.3.4 Metallic nickel

Intratracheal administration of metallic nickel powder caused lung tumours in rats ([Pott et al., 1987](#)). Metallic nickel also caused local tumours in rats when administered by injection (intrapleural, subcutaneous, intramuscular, and intraperitoneal) ([Hueper, 1952, 1955](#); [Mitchell et al., 1960](#); [Heath & Daniel, 1964](#); [Furst & Schlauder, 1971](#); [Berry et al., 1984](#); [Sunderman, 1984](#); [Judde et al., 1987](#); [Pott et al., 1987, 1990](#)).

3.3.5 Nickel sulfate

Nickel sulfate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats ([Pott et al., 1989, 1990](#)).

Table 3.3 Studies of cancer in experimental animals exposed to nickel compounds (parenteral administration and intratracheal instillation)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Mouse, Strain A (M) 45 wk McNeill et al. (1990)	i.t. and i.p. 0, 0.53, 0.160 mg/kg bw 3 dosing regimens for 15 wk 1/wk (15 treatments), 1 every 2 wk (8 treatments), 1 every 3 wk (5 treatments); 3 doses per regiment; 30/group 10 mice sacrificed after 20 wk	Lung (adenomas at 45 wk ⁺): i.t. – Number of treatments: dose 5: 68%, 63%, 58% 8: 64%, 54%, 61% 15: 47%, 47%, 56% i.p. – 5: 68%, 63%, 53% 8: 58%, 53%, 63% 15: 63%, 47%, 50%		Age at start, 8–10 wk Nickel subsulfide –1.8 µm mass medium diameter 73% Nickel and 26.3% sulfur (weight) Urethane (positive control) significantly increased tumour incidence i.p., i.t., after 20 wk, and i.t. after 45 wk, average. number of adenoma/mouse increased i.p. and i.t. at both time points No treatment effects on bw
Mouse, C57BL/6, B6C3F ₁ , CeH/He (M) 78 wk Rodriguez et al. (1996)	i.m. (thigh) 0, 0.5, 1.0, 2.5, 5.0, 10 mg/site (single injection) 30/group	Injection site (rhabdomyosarcomas, fibrosarcomas, and other e.g. liposarcomas, haemangiosarcomas): C3He 0/30, 5/30 (16.6%), 10/30 (33.3%), 20/27 (74.1%), 28/29, (96.6%) 14/14 (100%) B6C3F ₁ 0/30, 2/29 (6.9%), 8/30 (26.7%), 15/30 (50.0%), 16/20 (80%), 5/6 (83.3%) C57BL 0/24, 1/27 (3.7%), 4/28 (14.3%), 6/21 (28.6%), 6/15 (40%), 0/2	 [P = 0.052, 0.5 mg; P < 0.001 for other doses] ^a [P < 0.01, 1.0 mg, P < 0.001, 2.5, 5.0, 10 mg] ^a [P < 0.01, 2.5, 5 mg] ^a	Age at start, 6–8 wk; weight, 23–29 g High dose was lethal within 1 wk to over 50% of all 3 strains; susceptibility was C57BL > B6C3F ₁ > C3H Treatment-related decrease in bw was observed for C3H and B6C3F ₁ at 2 highest doses. Tumours of the liver, lung adenomas and leukaemias were also observed, but were not increased in exposed groups compared to controls Susceptibility to tumours C3H > B6C3F ₁ > C57BL

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Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT transgenic and wild-type (M) 104 wk Waalkes et al. (2004)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection) 25/group	Injection site (primarily fibrosarcomas, but also included fibromas and lymphosarcomas): WT-0/24, 5/25 (20%), 10/25 (40%) MT-Tg-0/25, 7/25 (28%), 7/24 (29%) Lung (adenomas or adenocarcinomas): WT-6/24 (25%), 5/25 (20%), 9/25 (36%) MT-Tg-0/25, 3/25 (12%), 4/24 (17%)	WT: $P < 0.05$, mid-and low dose, $P_{\text{trend}} < 0.0001$ MT-Tg: $P < 0.05$, mid-and low dose, $P_{\text{trend}} = 0.0081$ trend MT-Tg: $P = 0.0502$ high dose $P_{\text{trend}} = 0.046$	Age at start, 12 wk 99.9% pure, 30 μm particles Average survival time less in MT-Tg mice than controls. Treatment- related decrease in survival in WT but not MT-Tg mice. No effect on bw No differences in injection-site tumour incidence or latency between MT-Tg and WT mice MT-transgenic controls had significantly lower incidence of lung tumours than WT controls.
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes et al. (2005)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection), 25/group	Injection site (primarily fibrosarcomas, but also included fibromas): WT-0/24, 8/25 (32.0%), 18/25 (72.0%) MT-null-0/24, 11/24 (45.8%), 15/23 (62.5%) Lung (adenomas or adenocarcinomas): WT-7/24 (29.2%), 12/25 (48.0%), 11/25 (44.0%) MT-null-10/24 (41.7%), 13/24 (54.2%), 4/23 (16.7%)	$P < 0.05$ low and high dose $P < 0.05$ low and high dose	Age at start, 12 wk 99.9% pure, < 30 μm particles No difference in survival between control MT-null mice and control WT mice. Nickel treatment reduced survival at later time points corresponding to the appearance of sarcomas. Nickel treatment reduced bw in high-and mid dose MT-null and high-dose WT mice

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalikes et al. (2005) (contd.)		Lung (adenocarcinomas): WT-1/24 (4.2%), 10/25 (40.0%), 3/25 (12.0%) MT-null-3/24 (12.5%), 3/24 (12.5%), 4/23 (17.4%) Lung (adenomas): WT-6/24 (25%), 2/25 (8.0%), 8/25 (32.0%) MT-null-7/24 (29.2%), 10/24 (41.7%), 0/23	WT: $P < 0.05$ low dose MT-null: $P < 0.05$ control vs high dose	
Rat, F344/NCr (M) 109 wk Kasprzak et al. (1994)	i.r. (2 injections) Ni_3S_2 - 5 mg, MgCarb - 6.2 mg, Fe^0 - 3.4 mg Groups: treatment, number of animals Group 1: Ni_3S_2 , 40 Group 2: Ni_3S_2 + MgCarb, 20 Group 3: MgCarb, 20 Group 4: Ni_3S_2 + Fe^0 , 20 Group 5: Fe^0 , 20 Group 6: vehicle, 20 20-40/group	Kidney (malignant tumours of mesenchymal cell origin) at 104 wk: Group 1: 25/40 (63%) Group 2: 4/20 (20%) Group 3: 0/20 Group 4: 12/20 (60%) Group 5: 0/20 Group 6: 0/20	Group 2 vs Group 1 [$P < 0.01$] ^a	$\text{Ni}_3\text{S}_2 < 10\mu\text{m}$ No effect on bw or survival (from causes other than kidney tumours) MgCarb also delayed onset of tumours (besides decreasing the incidence), and Fe decreased time until first tumour Metastases to lung, liver, spleen and other kidney

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Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/NCr (M) 109 wk Kasprzak & Ward (1991)	i.m. and s.c (single injection) Ni ₃ S ₂ – 2.5 mg, MB – 0.5 mg, CORT – 1.0 mg, IND – 1.0 mg. Groups: i.m., s.c., number of animals Group 1: Ni ₃ S ₂ , none, 20 Group 2: MB, none, 20 Group 3: Ni ₃ S ₂ + MB, none, 20 Group 4: CORT, none, 20 Group 5: Ni ₃ S ₂ + CORT, none, 20 Group 6: IND, none, 20 Group 7: Ni ₃ S ₂ + IND, none, 20 Group 8: water, none, 20 Group 9: Ni ₃ S ₂ , MB, 20 Group 10: Ni ₃ S ₂ , IND, 20 20/group	Injection-site tumours (rhabdomyosarcomas, fibrosarcomas, histolytic sarcomas): 36 wk; 71 wk Group 1: 10/20 (50%); 17/20 (85%) Group 2: 0/20; 0/20 Group 3: 0/20; 1/20 (5%) Group 4: 0/20; 0/20 Group 5: 9/20 (45%); 17/20 (85%) Group 6: 0/20; 0/20 Group 7: 6/20 (30%); 16/20 (80%) Group 8: 0/20; 0/20 Group 9: 18/20 (90%); 20/20 (100%) Group 10: 13/20 (65%); 19/20 (95%)	[Groups 2, 3, 4, 6 or 8 vs Group 1, 36 & 71 wk, <i>P</i> < 0.01; Group 9 vs Group 1, 36 wk, <i>P</i> < 0.05] ^a	Age at start, 8 wk Ni ₃ S ₂ < 10µm No effect on bw Metastases to the lung MB given away from the injection site (s.c.) decreased tumour latency induced by Ni ₃ S ₂

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (F) 1 yr Ohmori et al. (1990)	Ni ₃ S ₂ -10 mg Groups, treatment, number of animals Group 1: fracture bone, 10 mg/ fracture, 20 Group 2: 10 mg i.m right thigh, 20 Group 3: 10 mg i.a. right knee joint, 20 Group 4: control (CM), 3 fractured bone, 3 i.m., 2 i.a. 20/group	Injection site (malignant fibrous histiocytomas, rhabdomyosarcomas, fibrosarcomas, leiomyosarcomas): Group 1: 17/20 (85%) Group 2: 20/20 (100%) Group 3: 16/20 (80%) Group 4: 0/7 (0%) Metastasis (lymph node, lung): Group 1: 16/17 (94.1), 9/17 (52.9) Group 2: 5/20 (25.0%), 3/20 (15.0%) Group 3: 3/16 (18.8%), 2/16 (12.5%) Group 4: 0/7, 0/7	<i>P</i> < 0.05, Group 1 vs Group 2 or Group 3	Age at start, 10 wk Ni ₃ S ₂ medium particle diameter < 2µm Vehicle, CM Tumour-induction time and survival time shorter in Group 1 than Groups 2 or 3. No osteogenic sarcoma developed in bone-fracture group
Rat, Wistar (M, F) 70 wk Ohmori et al. (1999)	Ni ₃ S ₂ -10 mg i.m. (single injection) Groups, strain, treatment, number of animals Group 1: SHR-10 mg; 15F, 15M Group 2: CWR-10 mg; 15F, 16M Group 3: SHR-0 mg; 6F, 6M Group 4: CWR-0 mg 7F, 7M 6-15/group	Sarcomas (rhabdomyosarcomas, leiomyosarcomas, fibrosarcomas and malignant fibrous histiocytomas): Groups: F; M; Total Group 1: 2/15 (13.3%); 5/15 (33.3%); 7/30 (23.3%) Group 2: 8/15 (53.3%), 13/16 (81.4%); 21/31 (67.7%) Group 3: 0/6, 0/6 Group 4: 0/7, 0/7	Total: Group 1 vs Group 2, <i>P</i> < 0.005	Age, 10 wk Ni ₃ S ₂ medium particle diameter < 2µm Vehicle, CM Tumour incidence, progression (as shown by tumour size and metastasis) was significantly lower in SHR rats (M, F combined) than in CWR rats Metastases observed in the lung and lymph node

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Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M) 104 wk Sunderman et al. (1990)	i.m. (hind limb) single injection Group: Ni by wt.; other elements V: vehicle control (glycerol) A: 0.81% Ni (III); none B: 0.05% Ni (III); none F: < 0.03% Ni (III); none H: 21% Cu, 2% Fe, 1.1% Co, 1% S, 0.5% Ni ₃ S ₂ I: 13% Cu, 1.2% Fe, 1.0 Co, 0.3% S, 1.0% Ni ₃ S ₂ (positive control) 20 mg Ni/rat 15/group	Injection site (rhabdomyosarcomas, fibrosarcomas, malignant fibrous histiocytomas, leiomyosarcomas, undifferentiated): V, 0/15; A, 6/15 (40.0%); B, 0/15; F, 0/15; H, 13/15 (86.7%); I, 15/15 (100%) Positive control, Ni ₃ S ₂ 15/15 (100%) Metastases V: 0; A: 3; B: 0; F: 0; H: 4; I: 4 Ni ₃ S ₂ : 12 Other primary tumours V: 0; A: 0; B: 3; F: 0; H: 0; I: 3 Ni ₃ S ₂ : 0	$P < 0.01$ A; $P < 0.001$ H, I, Ni ₃ S ₂	Age at start, ~2 mo 5 NiO compounds – all compounds had 52–79% Nickel (total), and 22–24% O. Nickel could not be determined in Groups H and I because of the presence of sulfur Groups A, H, and I all had measurable dissolution rates in body fluids and were strongly positive in an erythrocytosis-stimulation assay Compounds B and F were insoluble in body fluids, did not stimulate erythrocytosis and had little Ni (III), Cu Fe, Co, or S
Rat, Wistar (F) Life span Pott et al. (1987)	(mg x wk) number of animals NiO 50 mg (10 x 5); 34 150 mg (10 x 15); 37 Ni ₃ S ₂ 0.94 mg (15 x 0.063); 47 1.88 mg (15 x 0.125); 45 3.75 mg (15 x 0.25); 47 Nickel powder 6 mg (20 x 0.3); 32 9 mg (10 x 0.9); 32 32–47/group	Lung (adenomas, adenocarcinomas, squamous cell carcinomas): % tumours for each dose NiO–27%, 31.6% Ni ₃ S ₂ –15%, 28.9% Nickel powder–25.6%, 25% Saline, 0%		Age at start, 11 wk NiO, 99.9% pure

Nickel and nickel compounds

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel acetate				
Rat, F344/NCr (M) 101 wk Kasprzak et al. (1990)	NiAcet -90 µmol/kg bw single i.p. injection NaBB-50 ppm in drinking-water (2 wk after NiAcet) Groups, treatment, # of animals Group 1: NiAcet, 23 Group 2: NiAcet + NaBB, 24 Group 3: NaBB, 24 Group 4: Saline, 24 24/group	Renal cortical tumours (adenomas & adenocarcinomas): Group 1-1/23 (4.3%) Group 2-16/24 (66.7%) (4 carcinomas) Group 3-6/24 (25%) Group 4-0/24 Renal pelvic tumours (papillomas & carcinomas): Group 1-0/23 Group 2-8/24 (33.3%) Group 3-13/24 (54.2%) (1 carcinoma) Group 4-0/24	$P < 0.008$ vs Group 3	Age at start, 5 wk Initiation/promotion study Decreased survival and bw in rats given nickel acetate followed by NaBB Kidney weight increased in Groups 2 and 3 Renal cortical tumours: metastatic nodules observed in the lung, spleen and liver
Mouse, Strain A (M, F) 30 wk Stoner et al. (1976)	i.p. Nickel acetate 3x/wk (24 injections total) 0, 72, 180, 360 mg/kg Saline control 20/group	Lung (adenomas): Average number of tumours/ mouse (mean ± SD) Saline: 0.42 ± 0.10 72: 0.67 ± 0.16 180: 0.71 ± 0.19 360: 1.26 ± 0.29	$P < 0.01$ high dose	Age at start, 6-8 wk 99.9% pure Sample of nodules confirmed by histopathology No difference in control M, F, so M, F were combined Positive control urethane Control saline Doses correspond to MTD, ½ MTD, 1/5 MTD
Mouse, Strain A (M, F) 30 wk Poirier et al. (1984)	i.p. Nickel acetate 10.7 mg/kg bw (0.04 mmol kg/bw)/injection 3x/wk (24 injections total) 30/group/sex	Lung (adenomas): Average number of tumours/ mouse (mean ± SD) Saline: 0.32 ± 0.12 Nickel acetate: 1.50 ± 0.46	$P < 0.05$	Age at start, 6-8 wk Nodules (sample) confirmed by histology Co-exposure to calcium and magnesium decreased multiplicity

^a Calculated by Fisher Exact Test, Significance not reported by authors
bw, body weight; CM, chloromycetin; CORT, cortisol; CWR, common closed colony rats; F, female; Fe⁰, metallic iron; HSR, spontaneously hypertensive rats; i.a., intra-articular; i.f., intra-fat; i.m., intramuscular; IND, indometacin; i.p., intraperitoneal; i.r., intratracheal instillation; M, male; MB, *Mycobacterium bovis* antigen; MgCarb, magnesium basic carbonate; MT, metallothionin; MTD, maximum tolerated dose; NaBB, sodium barbital; Ni, nickel; NiAcet, nickel acetate; Ni₃S₂, nickel subsulfide; s.c., subcutaneous; SD, standard deviation; Tg, Transgenic; wk, week or weeks; WT, wild type; yr, year or years

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Table 3.4 Studies of cancer in experimental animals exposed to nickel acetate (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Target organs	Significance	Comments
Rat, F344/NCr (M, F) 85 wk Diwan et al. (1992)	<p><i>Dams – i.p.</i> NiAcet (90 µmol/kg wt total) Group: µmol/kg bw; regimen Group 1: 90; once at Day 17 of gestation Group 2: 45; twice at Days 16 & 18 of gestation Group 3: 45; 4 times at Days 12, 14, 16, 18 of gestation Group 4: control (180 NaAcet) once at Day 18 of gestation <i>Offspring 4 to 85 wk (drinking-water) ad libitum</i> 1A, 2A, 4A – tap water 1B, 2B, 4B – 0.05% NBB</p>	<p>Renal tumours (cortex adenomas and carcinomas; or pelvis papillomas and carcinomas): 1A: 0/17 (M), 0/16 (F) 2A: 0/15 (M), 0/15 (F) 4A: 0/15 (M), 0/16 (F) 1B: 8/15 (53.3%, M), 0/15 (F) 2B: 7/15 (46.7%, M), 0/15 (F) 4B: 1/15 (6.67%, M), 0/14 (F) Pituitary gland (adenomas or carcinomas): 1A: 9/17 (52.9%, M), 5/16 (31.3%, F), 14/33 (42.3%, M, F) 2A: 6/15 (40.0%, M), 8/16 (50%, F), 14/31 (45.2%, M, F) 4A: 1/15 (6.7%, M), 3/14 (21.4%, F) 1B: 6/15 (40.0%, M), 5/15 (33.3%, F) 2B: 7/15 (46.7%, M), 6/15 (40.0%, F) 4B: 2/15 (13.3%, M), 4/14 (28.6%, F)</p>	<p>M: $P = 0.007$ (1B vs 4B) M: $P = 0.012$ (2B vs 4B) M, F: $P = 0.12$ 1A vs 4A M, F: $P = 0.008$ 2A vs 4A</p>	<p>Dams, age at start 3–4 mo Purity not provided Male (Groups 1 & 2) – significantly decreased bw at 75 wk All offspring in Group 3 died at 72 h. Survival was decreased in Groups 1A, 1B, 2A and 2B compared to controls (4A and 4B) Pituitary tumours: significantly decreased latency for Groups 1A (M, F), 1B (M, F) and 2A (F) compared to the Groups 4A or 4B (corresponding M or F)</p>

h, hour or hours; F, female; i.p., intraperitoneal; M, male; mo, month or months; NaBB, sodium barbital; vs, versus; wk, week or weeks

3.3.6 Nickel chloride

Nickel chloride induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats ([Pott et al., 1989, 1990](#)).

3.3.7 Other forms of nickel

Intramuscular administration of nickel sulfarsenide, nickel arsenides, nickel antimonide, nickel telluride, and nickel selenides caused local sarcomas in rats ([Sunderman & McCully, 1983](#)). Intramuscular administration of nickelocene caused some local tumours in rats and hamsters ([Furst & Schlauder, 1971](#)).

3.4 Transplacental exposure

3.4.1 Nickel acetate

[Diwan et al. \(1992\)](#) studied the carcinogenic effects of rats exposed transplacentally to nickel acetate and postnatally to sodium barbital in drinking-water. Pregnant F344 were given nickel acetate by intraperitoneal injection, and their offspring were divided into groups receiving either tap water or sodium barbital in drinking-water. An increased incidence in pituitary tumours was observed in the offspring of both sexes transplacentally exposed to nickel acetate. These tumours were mainly malignant, and are rare tumours. Renal tumours were observed in the male offspring exposed transplacentally to nickel acetate, and receiving sodium barbital postnatally, but not in the male offspring receiving tap water after nickel *in utero*.

See [Table 3.4](#).

3.5 Synthesis

The inhalation of nickel oxide, nickel subsulfide, and nickel carbonyl caused lung tumours in rats. Intratracheal instillation of nickel oxide, nickel subsulfide, and metallic nickel

caused lung tumours in rats. Lung tumours were observed by the intraperitoneal injection of nickel acetate in two studies in A/J mice, and by intramuscular injection of nickel subsulfide in mice. The inhalation of nickel oxide, nickel subsulfide, and metallic nickel caused adrenal medulla pheochromocytoma in rats. Transplacental nickel acetate induced malignant pituitary tumours in the offspring in rats. Several nickel compounds (nickel oxides, nickel sulfides, including nickel subsulfide, nickel sulfate, nickel chloride, nickel acetate, nickel sulfarsenide, nickel arsenide, nickel antimonide, nickel telluride, nickel selenide, nickelocene, and metallic nickel) administered by repository injection caused sarcomas in multiple studies. The inhalation of metallic nickel did not cause lung tumours in rats. The inhalation and oral exposure to nickel sulfate did not cause tumours in rats or mice. The inhalation of nickel subsulfite did not cause tumours in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In rodents, nickel salts and nickel sulfides are absorbed through the lungs and excreted mainly in the urine ([Benson et al., 1994, 1995a](#)). After inhalation exposure to green nickel oxide, nickel is not distributed in extrapulmonary tissues, and is excreted only in faeces ([Benson et al., 1994](#)). In humans, soluble nickel compounds are rapidly absorbed through the lungs, and excreted in the urine. After inhalation exposure to insoluble nickel species, elevated concentrations of nickel are observed in the plasma and urine, but the absorption is slow ([Bernacki et al., 1978](#); [Tola et al., 1979](#)).

In rats exposed to nickel sulfate hexahydrate by inhalation for 6 months or 2 years,

no pulmonary accumulation is observed; in a similar exposure scenario with nickel subsulfide, concentrations of nickel are detected in the lungs, with very slight nickel accumulation. Following the exposure of green nickel oxide to rats, the nickel lung clearance half-life is approximately 130 days, and in long-term exposure (NTP, 1996a, b, c; described in Section 3), a remarkable accumulation of nickel is observed (Benson *et al.*, 1995b; Dunnick *et al.*, 1995). The lung clearance half-life of nanoparticulate black nickel oxide in rats is reported as 62 days (Oyabu *et al.*, 2007). The difference in the two clearance rates may be related to the greater water solubility (and the smaller particle size) of the nanoparticulate black nickel oxide. In mice, the observed clearance for nickel sulfate is fast, but for nickel subsulfide intermediate and for green nickel oxide, very slow (Dunnick *et al.*, 1995).

4.1.1 Cellular uptake

Nickel chloride has been shown in different cell lines in culture to be transported to the nucleus (Abbracchio *et al.*, 1982; Edwards *et al.*, 1998; Ke *et al.*, 2006, 2007; Schwerdtle & Hartwig, 2006). Soluble nickel chloride compounds enter cells via the calcium channels and by metal ion transporter 1 (Refsvik & Andreassen, 1995; Funakoshi *et al.*, 1997; Gunshin *et al.*, 1997; Garrick *et al.*, 2006). Crystalline nickel sulfides are phagocytized by a large variety of different cells in culture (Kuehn *et al.*, 1982; Miura *et al.*, 1989; Hildebrand *et al.*, 1990, 1991; IARC, 1990).

Black nickel oxide and nickel chloride are taken up by human lung carcinoma cell lines A549 in culture; the nucleus/cytoplasm ratio is > 0.5 for black nickel oxide, and < 0.18 for nickel chloride (Fletcher *et al.*, 1994; Schwerdtle & Hartwig, 2006).

After phagocytosis of nickel subsulfide, intracellular nickel containing particles rapidly dissolve, and lose sulfur (Arrouijal *et al.*, 1990; Hildebrand *et al.*, 1990, 1991; Shirali *et al.*, 1991).

4.2 Genetic and related effects

The mechanisms of the carcinogenicity of nickel compounds have been reviewed extensively (Hartwig *et al.*, 2002; Zoroddu *et al.*, 2002; Costa *et al.*, 2003, 2005; Harris & Shi, 2003; Kasprzak *et al.*, 2003; Lu *et al.*, 2005; Durham & Snow, 2006; Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008).

Based on the uptake and distribution in cells described above, the ultimate genotoxic agent is Ni (II). However, direct reaction of Ni (II) with DNA does not seem to be relevant under realistic exposure conditions. Nevertheless, nickel is a redox-active metal that may, in principle, catalyse Fenton-type reactions, and thus generate reactive oxygen species (Nackerdien *et al.*, 1991; Kawanishi *et al.*, 2001). Genotoxic effects have been consistently observed in exposed humans, in experimental animals, and in cell culture systems, and include oxidative DNA damage, chromosomal damage, and weak mutagenicity in mammalian cells. These effects are likely to be due to indirect mechanisms, as described in detail below.

4.2.1 Direct genotoxicity

(a) DNA damage

Water-soluble as well as water-insoluble nickel compounds induce DNA strand breaks and DNA protein crosslinks in different mammalian test systems, including human lymphocytes. Nevertheless, in the case of DNA strand breaks and oxidative DNA lesions, these events mainly occur with conditions that involve comparatively high cytotoxic concentrations (IARC, 1990; Pool-Zobel *et al.*, 1994; Dally & Hartwig, 1997; Cai & Zhuang, 1999; Chen *et al.*, 2003; M'Bemba-Meka *et al.*, 2005; Schwerdtle & Hartwig, 2006; Caicedo *et al.*, 2007). This is also true for the induction of oxidative DNA base modifications in cellular systems. Nevertheless, oxidative DNA damage is also observed in experimental animals, this may

be due to repair inhibition of endogenous oxidative DNA damage.

The intratracheal instillation of several soluble and insoluble nickel compounds to rats significantly increases 8-hydroxydeoxyguanine (8-OH-dG) content in the lungs. Concomitantly, microscopic signs of inflammation in the lungs are also observed. Two distinct mechanisms are proposed: one via an inflammatory reaction and the other through cell-mediated reactive oxygen species formation ([Kawanishi et al., 2001](#); [Kawanishi et al., 2002](#)).

(b) Chromosomal alterations

Water-soluble and poorly water-soluble nickel compounds induce sister chromatid exchange and chromosomal aberrations at toxic levels in different mammalian test systems ([Conway et al., 1987](#); [Conway & Costa, 1989](#); [IARC, 1990](#); [Howard et al., 1991](#)). Chromosomal aberrations are most pronounced in heterochromatic chromosomal regions ([Conway et al., 1987](#)). Water-soluble and poorly water-soluble nickel compounds induce micronuclei at comparatively high concentrations. Because increases in both kinetochore-positive and -negative micronuclei are observed, these effects are likely due to aneugenic as well as clastogenic actions ([Arroujjal et al., 1990, 1992](#); [Hong et al., 1997](#); [Seoane & Dulout, 2001](#)). The induction of chromosomal aberrations and micronuclei in rodents treated with different nickel compounds is not consistent across studies ([Sobti & Gill, 1989](#); [Arroujjal et al., 1990](#); [Dhir et al., 1991](#); [IARC, 1990](#); [Oller & Erexson, 2007](#)). Enhanced frequencies of chromosomal aberrations were observed in some studies in lymphocytes of nickel-exposed workers ([IARC, 1990](#)).

(c) Gene mutations in bacterial and mammalian test systems

Nickel compounds are not mutagenic in bacterial test systems, and are only weakly mutagenic in cultured mammalian cells. Even though, mutagenic responses for both water-soluble and

water-insoluble nickel compounds have been reported in transgenic G12 cells, this effect was later shown to result from epigenetic gene-silencing ([Lee et al., 1995](#)). Nevertheless, the prolonged culture of V79 cells after treatment with nickel sulfate results in the appearance of genetically unstable clones with high mutation rates together with chromosomal instability ([Little et al., 1988](#); [Ohshima, 2003](#)).

(d) Cell transformation

Water-soluble and poorly water-soluble nickel compounds induced anchorage-independent growth in different cell systems ([IARC, 1990](#)), including the mouse-embryo fibroblast cell-line PW and the human osteoblast cell line HOS-TE85 ([Zhang et al., 2003](#)). Nickel compounds were shown to cause morphological transformation in different cell types ([Conway & Costa, 1989](#); [Miura et al., 1989](#); [Patierno et al., 1993](#); [Lin & Costa, 1994](#)).

4.2.2 Indirect effects related to genotoxicity

As stated above, the direct interaction of nickel compounds with DNA appears to be of minor importance for inducing a carcinogenic response. However, several indirect mechanisms have been identified, which are discussed below.

(a) Oxidative stress

Treatment with soluble and insoluble nickel causes increases in reactive oxygen species in many cell types ([Huang et al., 1993](#); [Salnikow et al., 2000](#); [Chen et al., 2003](#)).

Increased DNA strand breaks, DNA-protein crosslinks and sister chromatid exchange are found in cells treated with soluble and insoluble nickel compounds, and these are shown to result from the increase in reactive oxygen species ([Chakrabarti et al., 2001](#); [Błasiak et al., 2002](#); [Woźniak & Błasiak, 2002](#); [M'Bemba-Meka et al., 2005, 2007](#)).

Intraperitoneal injection of nickel acetate in rat did not cause any DNA damage in liver and kidney at 12 hours. However, oxidative DNA damage increased after 24 hours, and persisted in the kidney for 14 days ([Kasprzak et al., 1997](#)).

(b) *Inhibition of DNA repair*

The treatment of cells with soluble Ni (II) increases the DNA damage and the mutagenicity of various agents ([Hartwig & Beyersmann, 1989](#); [Snyder et al., 1989](#); [Lee-Chen et al., 1993](#)).

Soluble Ni (II) inhibits nucleotide-excision repair after UV irradiation, and the effect seems to be on the incision, the polymerization, and ligation steps in this pathway ([Hartwig et al., 1994](#); [Hartmann & Hartwig, 1998](#); [Woźniak & Błasiak, 2004](#)). One of the proteins in nucleotide-excision repair, the XPA protein, may be a target of Ni (II) ([Asmuss et al., 2000a, b](#)).

Soluble nickel chloride also inhibits base-excision repair. The base-excision repair enzyme, 3-methyladenine-DNA glycosylase II, is inhibited specifically ([Dally & Hartwig, 1997](#); [Woźniak & Błasiak, 2004](#); [Wang et al., 2006](#)).

There is some evidence that the enzyme O⁶-methylguanine-DNA methyltransferase (MGMT) is inhibited by nickel chloride ([Iwitzki et al., 1998](#)).

(c) *Epigenetic mechanisms*

Both water-soluble and water-insoluble nickel compounds are able to cause gene silencing ([Costa et al., 2005](#)). This effect was first found when “mutations” in the transgenic *gpt* gene in G12 cells were found to be epigenetically silenced rather than mutated ([Lee et al., 1995](#)). Genes that are located near heterochromatin are subject to such inactivation by nickel. The *gpt* gene was silenced by DNA methylation. Additional studies show that cells treated with nickel have decreased histone acetylation, and altered histone methylation patterns ([Golebiowski & Kasprzak, 2005](#); [Chen et al., 2006](#)). Nickel also causes ubiquitination and phosphorylation of histones ([Karaczyn](#)

[et al., 2006](#); [Ke et al., 2008a, b](#)). Permanent changes in gene expression are important in any mechanism of carcinogenesis.

4.3 Synthesis

The ultimate carcinogenic species in nickel carcinogenesis is the nickel ion Ni(II). Both water-soluble and poorly water-soluble nickel species are taken up by cells, the former by ion channels and transporters, the latter by phagocytosis. In the case of particulate compounds, nickel ions are gradually released after phagocytosis. Both water-soluble and -insoluble nickel compounds result in an increase in nickel ions in the cytoplasm and the nucleus. Nickel compounds are not mutagenic in bacteria, and only weakly mutagenic in mammalian cells under standard test procedures, but can induce DNA damage, chromosomal aberrations, and micronuclei *in vitro* and *in vivo*. However, delayed mutagenicity and chromosomal instability are observed a long time after treatment of cells with nickel. Nickel compounds act as co-mutagens with a variety of DNA-damaging agents. Thus, disturbances of DNA repair appear to be important. A further important mechanism is the occurrence of epigenetic changes, mediated by altered DNA methylation patterns, and histone modification. Inflammation may also contribute to nickel-induced carcinogenesis.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal. These agents cause cancers of the lung and of the nasal cavity and paranasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nickel monoxides, nickel hydroxides, nickel sulfides (including

nickel subsulfide), nickel acetate, and nickel metal.

There is *limited evidence* in experimental animals for the carcinogenicity of nickelocene, nickel carbonyl, nickel sulfate, nickel chloride, nickel arsenides, nickel antimonide, nickel selenides, nickel sulfarsenide, and nickel telluride.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel titanate, nickel trioxide, and amorphous nickel sulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of nickel compounds and nickel metal.

Nickel compounds are *carcinogenic to humans* (Group 1).

References

- Abbracchio MP, Simmons-Hansen J, Costa M (1982). Cytoplasmic dissolution of phagocytized crystalline nickel sulfide particles: a prerequisite for nuclear uptake of nickel. *J Toxicol Environ Health*, 9: 663–676. doi:10.1080/15287398209530194 PMID:7108981
- Albert DM, Gonder JR, Papale J *et al.* (1982). *Induction of ocular neoplasms in Fischer rats by intraocular injection of nickel subsulfide*. In: *Nickel Toxicology*. London: Academic Press, pp. 55–58.
- Andersen A, Berge SR, Engeland A, Norseth T (1996). Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occup Environ Med*, 53: 708–713. doi:10.1136/oem.53.10.708 PMID:8943837
- Antonsen DH, Meshri DT (2005). *Nickel compounds*. In: *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed. New York: John Wiley & Sons, 16:1–28.
- Anttila A, Pukkala E, Aitio A *et al.* (1998). Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. *Int Arch Occup Environ Health*, 71: 245–250. doi:10.1007/s004200050276 PMID:9638480
- Arena VC, Sussman NB, Redmond CK *et al.* (1998). Using alternative comparison populations to assess occupation-related mortality risk. Results for the high nickel alloys workers cohort. *J Occup Environ Med*, 40: 907–916. doi:10.1097/00043764-199810000-00012 PMID:9800177
- Arrouijal FZ, Hildebrand HF, Vopfi H, Marzin D (1990). Genotoxic activity of nickel subsulphide alpha-Ni3S2. *Mutagenesis*, 5: 583–589. doi:10.1093/mutage/5.6.583 PMID:2263215
- Arrouijal FZ, Marzin D, Hildebrand HF *et al.* (1992). Differences in genotoxic activity of alpha-Ni3S2 on human lymphocytes from nickel-hypersensitized and nickel-unsensitized donors. *Mutagenesis*, 7: 183–187. doi:10.1093/mutage/7.3.183 PMID:1602972
- Asmuss M, Mullenders LH, Eker A, Hartwig A (2000a). Differential effects of toxic metal compounds on the activities of Fpg and XPA, two zinc finger proteins involved in DNA repair. *Carcinogenesis*, 21: 2097–2104. doi:10.1093/carcin/21.11.2097 PMID:11062174
- Asmuss M, Mullenders LH, Hartwig A (2000b). Interference by toxic metal compounds with isolated zinc finger DNA repair proteins. *Toxicol Lett*, 112–113: 227–231. doi:10.1016/S0378-4274(99)00273-8 PMID:10720735
- ATSDR (2005). *Toxicological Profile for Nickel*. Atlanta, GA: US Public Health Service, Agency for Toxic Substances and Disease Registry.
- Barbante C, Boutron C, Moreau A-L *et al.* (2002). Seasonal variations in nickel and vanadium in Mont Blanc snow and ice dated from the 1960s and 1990s. *J Environ Monit*, 4: 960–966. doi:10.1039/b208142c PMID:12509051
- Basketter DA, Angelini G, Ingber A *et al.* (2003). Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. *Contact Dermatitis*, 49: 1–7. doi:10.1111/j.0105-1873.2003.00149.x PMID:14641113
- Bavazzano P, Bolognesi R, Cassinelli C *et al.* (1994). Skin contamination and low airborne nickel exposure of electroplaters. *Sci Total Environ*, 155: 83–86. PMID:7973613
- Benson JM, Barr EB, Bechtold HA *et al.* (1994). Fate of Inhaled Nickel Oxide and Nickel Subsulfide in F344/N Rats. *Inhal Toxicol*, 6: 167–183. doi:10.3109/08958379409029703
- Benson JM, Chang IY, Cheng YS *et al.* (1995a). Particle clearance and histopathology in lungs of F344/N rats and B6C3F1 mice inhaling nickel oxide or nickel sulfate. *Fundam Appl Toxicol*, 28: 232–244. doi:10.1006/faat.1995.1164 PMID:8835233
- Benson JM, Cheng YS, Eidson AF *et al.* (1995b). Pulmonary toxicity of nickel subsulfide in F344/N rats exposed for 1–22 days. *Toxicology*, 103: 9–22. doi:10.1016/0300-483X(95)03098-Z PMID:8525492
- Bernacki EJ, Parsons GE, Roy BR *et al.* (1978). Urine nickel concentrations in nickel-exposed workers. *Ann Clin Lab Sci*, 8: 184–189. PMID:655606
- Berry JP, Galle P, Poupon MF *et al.* (1984). Electron microprobe in vitro study of interaction of carcinogenic nickel compounds with tumour cells. *IARC Sci Publ*, 53153–164. PMID:6099827
- Beyersmann D & Hartwig A (2008). Carcinogenic metal compounds: recent insight into molecular and cellular

IARC MONOGRAPHS – 100C

- mechanisms. *Arch Toxicol*, 82: 493–512. doi:10.1007/s00204-008-0313-y PMID:18496671
- Błasiak J, Arabski M, Pertyński T *et al.* (2002). DNA damage in human colonic mucosa cells evoked by nickel and protective action of quercetin - involvement of free radicals? *Cell Biol Toxicol*, 18: 279–288. doi:10.1023/A:1016059112829 PMID:12206140
- Burges DCL (1980). *Mortality study of nickel platers*. In: *Nickel Toxicology*. Brown, S.S. & Sunderman, F.W., Jr, editors. London: Academic Press, pp. 1–18.
- Cai Y & Zhuang Z (1999). DNA damage in human peripheral blood lymphocyte caused by nickel and cadmium *Zhonghua Yu Fang Yi Xue Za Zhi*, 33: 75–77. PMID:11864456
- Caicedo M, Jacobs JJ, Reddy A *et al.* (2007). Analysis of metal ion-induced DNA damage, apoptosis, and necrosis in human (Jurkat) T-cells demonstrates Ni(2+) and V(3+) are more toxic than other metals: Al(3+), Be(2+), Co(2+), Cr(3+), Cu(2+), Fe(3+), Mo(5+), Nb(5+), Zr(2+). *J Biomed Mater Res A*, 86: 905–913.
- CAREX Canada (2011). Available at: http://www.carexcanada.ca/en/nickel/occupational_exposure_estimates/phase_2/
- Chakrabarti SK, Bai C, Subramanian KS (2001). DNA-protein crosslinks induced by nickel compounds in isolated rat lymphocytes: role of reactive oxygen species and specific amino acids. *Toxicol Appl Pharmacol*, 170: 153–165. doi:10.1006/taap.2000.9097 PMID:11162780
- Chen CY, Wang YF, Huang WR, Huang YT (2003). Nickel induces oxidative stress and genotoxicity in human lymphocytes. *Toxicol Appl Pharmacol*, 189: 153–159. doi:10.1016/S0041-008X(03)00086-3 PMID:12791300
- Chen H, Ke Q, Kluz T *et al.* (2006). Nickel ions increase histone H3 lysine 9 dimethylation and induce transgene silencing. *Mol Cell Biol*, 26: 3728–3737. doi:10.1128/MCB.26.10.3728-3737.2006 PMID:16648469
- Conway K & Costa M (1989). Nonrandom chromosomal alterations in nickel-transformed Chinese hamster embryo cells. *Cancer Res*, 49: 6032–6038. PMID:2790817
- Conway K, Wang XW, Xu LS, Costa M (1987). Effect of magnesium on nickel-induced genotoxicity and cell transformation. *Carcinogenesis*, 8: 1115–1121. doi:10.1093/carcin/8.8.1115 PMID:3301046
- Costa M, Davidson TL, Chen H *et al.* (2005). Nickel carcinogenesis: epigenetics and hypoxia signalling. *Mutat Res*, 592: 79–88. PMID:16009382
- Costa M, Yan Y, Zhao D, Salnikow K (2003). Molecular mechanisms of nickel carcinogenesis: gene silencing by nickel delivery to the nucleus and gene activation/inactivation by nickel-induced cell signalling. *J Environ Monit*, 5: 222–223. doi:10.1039/b210260a PMID:12729258
- Cox JE, Doll R, Scott WA, Smith S (1981). Mortality of nickel workers: experience of men working with metallic nickel. *Br J Ind Med*, 38: 235–239. PMID:7272235
- Cragle DL, Hollis DR, Newport TH, Shy CM (1984). A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge Gaseous Diffusion Plant. *IARC Sci Publ*, 5357–63. PMID:6532993
- Creely KS, Aitken RJ (2008). Characterization of nickel industry workplace aerosols by particle size and nickel species. Research Report TM/07/03. January 2008. Edinburgh: Institute of Occupational Medicine
- Dally H & Hartwig A (1997). Induction and repair inhibition of oxidative DNA damage by nickel(II) and cadmium(II) in mammalian cells. *Carcinogenesis*, 18: 1021–1026. doi:10.1093/carcin/18.5.1021 PMID:9163690
- Dhir H, Agarwal K, Sharma A, Talukder G (1991). Modifying role of *Phyllanthus emblica* and ascorbic acid against nickel clastogenicity in mice. *Cancer Lett*, 59: 9–18. doi:10.1016/0304-3835(91)90129-6 PMID:1878862
- Diwan BA, Kasprzak KS, Rice JM (1992). Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. *Carcinogenesis*, 13: 1351–1357. doi:10.1093/carcin/13.8.1351 PMID:1499087
- Dunnick JK, Elwell MR, Radovsky AE *et al.* (1995). Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung. *Cancer Res*, 55: 5251–5256. PMID:7585584
- Durham TR & Snow ET (2006). Metal ions and carcinogenesis. *EXS*, 96: 97–130. PMID:16383016
- Easton DF, Peto J, Morgan LG *et al.* (1992). *Respiratory cancer mortality in Welsh nickel refiners: Which nickel compounds are responsible?* In: *Nickel and human health: current perspectives. Advances in environmental sciences and technology*. Niebor E, Nrigau J, editors. New York: Wiley & Sons, pp. 603–619.
- Edwards DL, Wataha JC, Hanks CT (1998). Uptake and reversibility of uptake of nickel by human macrophages. *J Oral Rehabil*, 25: 2–7. doi:10.1046/j.1365-2842.1998.00197.x PMID:9502120
- Egedahl R, Carpenter M, Lundell D (2001). Mortality experience among employees at a hydrometallurgical nickel refinery and fertiliser complex in Fort Saskatchewan, Alberta (1954–95). *Occup Environ Med*, 58: 711–715. doi:10.1136/oem.58.11.711 PMID:11600726
- Enterline PE & Marsh GM (1982). Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. *J Natl Cancer Inst*, 68: 925–933. PMID:6953273
- EVM (2002). *Expert Group on Vitamins and Minerals: Revised Review of Nickel*. EVM/99/24.
- Fletcher GG, Rossetto FE, Turnbull JD, Nieboer E (1994). Toxicity, uptake, and mutagenicity of particulate and

- soluble nickel compounds. *Environ Health Perspect*, 102: Suppl 369–79. doi:10.2307/3431766 PMID:7843140
- Funakoshi T, Inoue T, Shimada H, Kojima S (1997). The mechanisms of nickel uptake by rat primary hepatocyte cultures: role of calcium channels. *Toxicology*, 124: 21–26. doi:10.1016/S0300-483X(97)00131-5 PMID:9392452
- Furst A & Schlauder MC (1971). The hamster as a model for metal carcinogenesis. *Proc West Pharmacol Soc*, 14: 68–71.
- Garrick MD, Singleton ST, Vargas F *et al.* (2006). DMT1: which metals does it transport? *Biol Res*, 39: 79–85. doi:10.4067/S0716-97602006000100009 PMID:16629167
- Gilman JP (1962). Metal carcinogenesis. II. A study on the carcinogenic activity of cobalt, copper, iron, and nickel compounds. *Cancer Res*, 22: 158–162. PMID:13898693
- Gilman JP (1966). Muscle tumourigenesis. *Proc Can Cancer Conf*, 6: 209–223. PMID:5972980
- Godbold JH Jr & Tompkins EA (1979). A long-term mortality study of workers occupationally exposed to metallic nickel at the Oak Ridge Gaseous Diffusion Plant. *J Occup Med*, 21: 799–806. PMID:556270
- Goldberg M, Goldberg P, Leclerc A *et al.* (1994). A 10-year incidence survey of respiratory cancer and a case-control study within a cohort of nickel mining and refining workers in New Caledonia. *Cancer Causes Control*, 5: 15–25. doi:10.1007/BF01830722 PMID:8123774
- Golebiowski F & Kasprzak KS (2005). Inhibition of core histones acetylation by carcinogenic nickel(II). *Mol Cell Biochem*, 279: 133–139. doi:10.1007/s11010-005-8285-1 PMID:16283522
- Grimsrud TK, Berge SR, Haldorsen T, Andersen A (2002). Exposure to different forms of nickel and risk of lung cancer. *Am J Epidemiol*, 156: 1123–1132. doi:10.1093/aje/kwf165 PMID:12480657
- Grimsrud TK, Berge SR, Haldorsen T, Andersen A (2005). Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? *Epidemiology*, 16: 146–154. doi:10.1097/01.ede.0000152902.48916.d7 PMID:15703528
- Grimsrud TK, Berge SR, Martinsen JI, Andersen A (2003). Lung cancer incidence among Norwegian nickel-refinery workers 1953–2000. *J Environ Monit*, 5: 190–197. doi:10.1039/b211722n PMID:12729252
- Grimsrud TK, Berge SR, Resmann SR *et al.* (2000). Assessment of historical exposures in a nickel refinery in Norway. *Scand J Work Environ Health*, 26: 338–345. PMID:10994800
- Grimsrud TK & Peto J (2006). Persisting risk of nickel related lung cancer and nasal cancer among Clydach refiners. *Occup Environ Med*, 63: 365–366. doi:10.1136/oem.2005.026336 PMID:16621856
- Gunshin H, Mackenzie B, Berger UV *et al.* (1997). Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature*, 388: 482–488. doi:10.1038/41343 PMID:9242408
- Harmse JL & Engelbrecht JC (2007). Air sampling of nickel in a refinery. *Int J Environ Health Res*, 17: 319–325. doi:10.1080/09603120701372698 PMID:17613095
- Harris GK & Shi X (2003). Signaling by carcinogenic metals and metal-induced reactive oxygen species. *Mutat Res*, 533: 183–200. PMID:14643420
- Hartmann M & Hartwig A (1998). Disturbance of DNA damage recognition after UV-irradiation by nickel(II) and cadmium(II) in mammalian cells. *Carcinogenesis*, 19: 617–621. doi:10.1093/carcin/19.4.617 PMID:9600346
- Hartwig A, Asmuss M, Ehleben I *et al.* (2002). Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. *Environ Health Perspect*, 110: Suppl 5797–799. PMID:12426134
- Hartwig A & Beyersmann D (1989). Enhancement of UV-induced mutagenesis and sister-chromatid exchanges by nickel ions in V79 cells: evidence for inhibition of DNA repair. *Mutat Res*, 217: 65–73. PMID:2911267
- Hartwig A, Mullenders LH, Schlepegrell R *et al.* (1994). Nickel(II) interferes with the incision step in nucleotide excision repair in mammalian cells. *Cancer Res*, 54: 4045–4051. PMID:8033135
- Heath JC & Daniel MR (1964). The production of malignant tumours by cadmium in the rat. *Br J Cancer*, 18: 124–129. PMID:14154225
- Heim KE, Bates HK, Rush RE, Oller AR (2007). Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats. *Toxicol Appl Pharmacol*, 224: 126–137. doi:10.1016/j.taap.2007.06.024 PMID:17692353
- Hildebrand HF, D'Hooghe MC, Shirali P *et al.* (1990). Uptake and biological transformation of beta NiS and alpha Ni3S2 by human embryonic pulmonary epithelial cells (L132) in culture. *Carcinogenesis*, 11: 1943–1950. doi:10.1093/carcin/11.11.1943 PMID:225326
- Hildebrand HF, Decaestecker AM, Arrouijal FZ, Martinez R (1991). In vitro and in vivo uptake of nickel sulfides by rat lymphocytes. *Arch Toxicol*, 65: 324–329. doi:10.1007/BF01968967 PMID:1953351
- Hong YC, Paik SR, Lee HJ *et al.* (1997). Magnesium inhibits nickel-induced genotoxicity and formation of reactive oxygen. *Environ Health Perspect*, 105: 744–748. doi:10.2307/3433730 PMID:9294721
- Horn-Ross PL, Ljung B-M, Morrow M (1997). Environmental factors and the risk of salivary gland cancer. *Epidemiol.*, 8: 414–419. doi:10.1097/00001648-199707000-00011 PMID:9209856
- Howard W, Leonard B, Moody W, Kochhar TS (1991). Induction of chromosome changes by metal compounds in cultured CHO cells. *Toxicol Lett*, 56: 179–186. doi:10.1016/0378-4274(91)90105-F PMID:2017776
- Huang X, Frenkel K, Klein CB, Costa M (1993). Nickel induces increased oxidants in intact cultured mammalian cells as detected by dichlorofluorescein

IARC MONOGRAPHS – 100C

- fluorescence. *Toxicol Appl Pharmacol*, 120: 29–36. doi:10.1006/taap.1993.1083 PMID:8511780
- Hueper WC (1952). Experimental studies in metal cancer-igenesis. I. Nickel cancers in rats. *Tex Rep Biol Med*, 10: 167–186. PMID:14922272
- Hueper WC (1955). Experimental studies in metal cancer-igenesis. IV. Cancer produced by parenterally intro-duced metallic nickel. *J Natl Cancer Inst*, 16: 55–73. PMID:13243113
- IARC (1973). Some inorganic and organometallic compounds. *IARC Monogr Eval Carcinog Risk Chem Man*, 2: 1–181.
- IARC (1976). Cadmium, nickel, some epoxides, miscella-neous industrial chemicals and general considerations on volatile anaesthetics. *IARC Monogr Eval Carcinog Risk Chem Man*, 11: 1–306. PMID:992654
- IARC (1979). Chemicals and industrial processes asso-ciated with cancer in humans: IARC Monographs volumes 1 to 20. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 1: 38
- IARC (1982). Cross index of synonyms and trade names in Volumes 1 to 26. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 3: 1–199. PMID:6959964
- IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 264–269. PMID:3482203
- IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49: 1–648. PMID:2232124
- International Committee on Nickel Carcinogenesis in Man. (1990). Report of the International Committee on Nickel Carcinogenesis in Man. *Scand J Work Environ Health*, 16: 1 Spec No1–82. PMID:2185539
- Iwitzki F, Schlepegrell R, Eichhorn U *et al.* (1998). Nickel(II) inhibits the repair of O6-methylguanine in mammalian cells. *Arch Toxicol*, 72: 681–689. doi:10.1007/s002040050561 PMID:9879805
- Järup L, Bellander T, Hogstedt C, Spång G (1998). Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. *Occup Environ Med*, 55: 755–759. PMID:9924452
- Jasmin G & Riopelle JL (1976). Renal carcinomas and erythrocytosis in rats following intrarenal injection of nickel subsulfide. *Lab Invest*, 35: 71–78. PMID:940323
- Judde JG, Breillout F, Clemenceau C *et al.* (1987). Inhibition of rat natural killer cell function by carcinogenic nickel compounds: preventive action of manganese. *J Natl Cancer Inst*, 78: 1185–1190. PMID:2438444
- Karaczyn AA, Golebiowski F, Kasprzak KS (2006). Ni(II) affects ubiquitination of core histones H2B and H2A. *Exp Cell Res*, 312: 3252–3259. doi:10.1016/j.yexcr.2006.06.025 PMID:16870173
- Karjalainen S, Kerttula R, Pukkala E (1992). Cancer risk among workers at a copper/nickel smelter and nickel refinery in Finland. *Int Arch Occup Environ Health*, 63: 547–551. doi:10.1007/BF00386344 PMID:1587630
- Kasprzak KS, Diwan BA, Konishi N *et al.* (1990). Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. *Carcinogenesis*, 11: 647–652. doi:10.1093/carcin/11.4.647 PMID:2323003
- Kasprzak KS, Diwan BA, Rice JM (1994). Iron accelerates while magnesium inhibits nickel-induced carcino-genesis in the rat kidney. *Toxicology*, 90: 129–140. doi:10.1016/0300-483X(94)90211-9 PMID:8023338
- Kasprzak KS, Gabryel P, Jarczewska K (1983). Carcinogenicity of nickel(II)hydroxides and nickel(II) sulfate in Wistar rats and its relation to the in vitro disso-lution rates. *Carcinogenesis*, 4: 275–279. doi:10.1093/carcin/4.3.275 PMID:6831634
- Kasprzak KS, Jaruga P, Zastawny TH *et al.* (1997). Oxidative DNA base damage and its repair in kidneys and livers of nickel(II)-treated male F344 rats. *Carcinogenesis*, 18: 271–277. doi:10.1093/carcin/18.2.271 PMID:9054618
- Kasprzak KS, Sunderman FW Jr, Salnikow K (2003). Nickel carcinogenesis. *Mutat Res*, 533: 67–97. PMID:14643413
- Kasprzak KS & Ward JM (1991). Prevention of nickel subsulfide carcinogenesis by local administration of Mycobacterium bovis antigen in male F344/NCr rats. *Toxicology*, 67: 97–105. doi:10.1016/0300-483X(91)90167-Y PMID:2017766
- Kawanishi S, Inoue S, Oikawa S *et al.* (2001). Oxidative DNA damage in cultured cells and rat lungs by carci-nogenic nickel compounds. *Free Radic Biol Med*, 31: 108–116. doi:10.1016/S0891-5849(01)00558-5 PMID:11425496
- Kawanishi S, Oikawa S, Inoue S, Nishino K (2002). Distinct mechanisms of oxidative DNA damage induced by carcinogenic nickel subsulfide and nickel oxides. *Environ Health Perspect*, 110: Suppl 5789–791. PMID:12426132
- Ke Q, Davidson T, Chen H *et al.* (2006). Alterations of histone modifications and transgene silencing by nickel chloride. *Carcinogenesis*, 27: 1481–1488. doi:10.1093/carcin/bgl004 PMID:16522665
- Ke Q, Davidson T, Kluz T *et al.* (2007). Fluorescent tracking of nickel ions in human cultured cells. *Toxicol Appl Pharmacol*, 219: 18–23. doi:10.1016/j.taap.2006.08.013 PMID:17239912
- Ke Q, Ellen TP, Costa M (2008a). Nickel compounds induce histone ubiquitination by inhibiting histone deubiquitinating enzyme activity. *Toxicol Appl Pharmacol*, 228: 190–199. doi:10.1016/j.taap.2007.12.015 PMID:18279901
- Ke Q, Li Q, Ellen TP *et al.* (2008b). Nickel compounds induce phosphorylation of histone H3 at serine 10 by activating JNK-MAPK pathway. *Carcinogenesis*, 29: 1276–1281. doi:10.1093/carcin/bgn084 PMID:18375956
- Kerfoot DGE (2002). Nickel. In: *Ullmann's Encyclopedia of Industrial Chemistry*. Wiley-VCH Verlag GmbH & Co.

Nickel and nickel compounds

- Kiilunen M (1997). Occupational exposure to chromium and nickel in the 1980s in Finland. *Sci Total Environ*, 199: 91–101. doi:10.1016/S0048-9697(97)05484-3 PMID:9200851
- Kiilunen M, Utela J, Rantanen T *et al.* (1997). Exposure to soluble nickel in electrolytic nickel refining. *Ann Occup Hyg*, 41: 167–188. PMID:9155238
- Kuck PH (2008). *Nickel*. In: *Mineral commodity summaries*. Reston, VA, US Geological Survey. Ref Type: Report
- Kuehn K, Fraser CB, Sunderman FW Jr (1982). Phagocytosis of particulate nickel compounds by rat peritoneal macrophages in vitro. *Carcinogenesis*, 3: 321–326. doi:10.1093/carcin/3.3.321 PMID:7083473
- Lee YW, Klein CB, Kargacin B *et al.* (1995). Carcinogenic nickel silences gene expression by chromatin condensation and DNA methylation: a new model for epigenetic carcinogens. *Mol Cell Biol*, 15: 2547–2557. PMID:7537850
- Lee-Chen SF, Wang MC, Yu CT *et al.* (1993). Nickel chloride inhibits the DNA repair of UV-treated but not methyl methanesulfonate-treated Chinese hamster ovary cells. *Biol Trace Elem Res*, 37: 39–50. doi:10.1007/BF02789400 PMID:7682828
- Leikauf GD (2002). Hazardous air pollutants and asthma. *Environ Health Perspect*, 110: Suppl 4505–526. PMID:12194881
- Lin X & Costa M (1994). Transformation of human osteoblasts to anchorage-independent growth by insoluble nickel particles. *Environ Health Perspect*, 102: Suppl 3289–292. doi:10.2307/3431804 PMID:7843117
- Little JB, Frenial JM, Coppey J (1988). Studies of mutagenesis and neoplastic transformation by bivalent metal ions and ionizing radiation. *Teratog Carcinog Mutagen*, 8: 287–292. doi:10.1002/tcm.1770080505 PMID:2905837
- Lu H, Shi X, Costa M, Huang C (2005). Carcinogenic effect of nickel compounds. *Mol Cell Biochem*, 279: 45–67. doi:10.1007/s11010-005-8215-2 PMID:16283514
- M'Bemba-Meka P, Lemieux N, Chakrabarti SK (2005). Nickel compound-induced DNA single-strand breaks in chromosomal and nuclear chromatin in human blood lymphocytes in vitro: role of oxidative stress and intracellular calcium. *Mutat Res*, 586: 124–137. PMID:16099703
- M'Bemba-Meka P, Lemieux N, Chakrabarti SK (2007). Role of oxidative stress and intracellular calcium in nickel carbonate hydroxide-induced sister-chromatid exchange, and alterations in replication index and mitotic index in cultured human peripheral blood lymphocytes. *Arch Toxicol*, 81: 89–99. doi:10.1007/s00204-006-0128-7 PMID:16826409
- Madrid L, Diaz-Barrientos E, Ruiz-Cortés E *et al.* (2006). Variability in concentrations of potentially toxic elements in urban parks from six European cities. *J Environ Monit*, 8: 1158–1165. doi:10.1039/b607980f PMID:17075623
- Magnus K, Andersen A, Høgetveit AC (1982). Cancer of respiratory organs among workers at a nickel refinery in Norway. *Int J Cancer*, 30: 681–685. PMID:7160938
- McNeill DA, Chrisp CE, Fisher GL (1990). Tumorigenicity of nickel subsulfide in Strain A/J mice. *Drug Chem Toxicol*, 13: 71–86. doi:10.3109/01480549009011070 PMID:2379474
- Minoia C, Sabbioni E, Apostoli P *et al.* (1990). Trace element reference values in tissues from inhabitants of the European community. I. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ*, 95: 89–105. doi:10.1016/0048-9697(90)90055-Y PMID:2402627
- Mitchell DF, Shankwalker GB, Shazer S (1960). Determining the tumorigenicity of dental materials. *J Dent Res*, 39: 1023–1028. doi:10.1177/00220345600390050401 PMID:13771327
- Miura T, Patierno SR, Sakuramoto T, Landolph JR (1989). Morphological and neoplastic transformation of C3H/10T1/2 Cl 8 mouse embryo cells by insoluble carcinogenic nickel compounds. *Environ Mol Mutagen*, 14: 65–78. doi:10.1002/em.2850140202 PMID:2548861
- Moulin JJ, Clavel T, Roy D *et al.* (2000). Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int Arch Occup Environ Health*, 73: 171–180. PMID:10787132
- Moulin JJ, Lafontaine M, Mantout B *et al.* (1995). Mortality due to bronchopulmonary cancers in workers of 2 foundries *Rev Epidemiol Sante Publique*, 43: 107–121. PMID:7732197
- Moulin JJ, Portefaix P, Wild P *et al.* (1990). Mortality study among workers producing ferroalloys and stainless steel in France. *Br J Ind Med*, 47: 537–543. PMID:2393634
- Moulin JJ, Wild P, Haguenoer JM *et al.* (1993b). A mortality study among mild steel and stainless steel welders. *Br J Ind Med*, 50: 234–243. PMID:8457490
- Moulin JJ, Wild P, Mantout B *et al.* (1993a). Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers. *Cancer Causes Control*, 4: 75–81. PMID:8386949
- Nackerdien Z, Kasprzak KS, Rao G *et al.* (1991). Nickel(II)- and cobalt(II)-dependent damage by hydrogen peroxide to the DNA bases in isolated human chromatin. *Cancer Res*, 51: 5837–5842. PMID:1933852
- National Institute for Occupational Safety and Health (NIOSH) (1990) *National Occupational Exposure Survey*.
- NTP (1996a). *NTP Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate (CAS No. 10101-97-0) in F344 Rats and B6C3F1 Mice (Inhalation Studies)*, 454:1–380.

IARC MONOGRAPHS – 100C

- NTP (1996b). *NTP Toxicology and Carcinogenesis Studies of Nickel Subsulfide* (CAS No. 12035-72-2) in F344 Rats and B6C3F1 Mice (*Inhalation Studies*), 453:1-365.
- NTP (1996c). *NTP Toxicology and Carcinogenesis Studies of Nickel Oxide* (CAS No. 1313-99-1) in F344 Rats and B6C3F1 Mice (*Inhalation Studies*), 451:1-381.
- NTP (2000). *Final Report on Carcinogens Background Document for Metallic Nickel and Certain Nickel Alloys*. Research Triangle Park, NC.
- Ohashi F, Fukui Y, Takada S *et al.* (2006). Reference values for cobalt, copper, manganese, and nickel in urine among women of the general population in Japan. *Int Arch Occup Environ Health*, 80: 117-126. doi:10.1007/s00420-006-0109-4 PMID:16736192
- Ohmori T, Okada K, Terada M, Tabei R (1999). Low susceptibility of specific inbred colonies of rats to nickel tumorigenesis in soft tissue. *Cancer Lett*, 136: 53-58. doi:10.1016/S0304-3835(98)00308-5 PMID:10211939
- Ohmori T, Uruga N, Komi K *et al.* (1990). The role of bone fracture at the site of carcinogen exposure on nickel carcinogenesis in the soft tissue. *Jpn J Cancer Res*, 81: 1247-1252. PMID:2125994
- Ohshima S (2003). Induction of genetic instability and chromosomal instability by nickel sulfate in V79 Chinese hamster cells. *Mutagenesis*, 18: 133-137. doi:10.1093/mutage/18.2.133 PMID:12621068
- Ojajärvi IA, Partanen TJ, Ahlbom A *et al.* (2000). Occupational exposures and pancreatic cancer: a meta-analysis. *Occup Environ Med*, 57: 316-324. doi:10.1136/oem.57.5.316 PMID:10769297
- Oliveira JP, de Siqueira ME, da Silva CS (2000). Urinary nickel as bioindicator of workers' Ni exposure in a galvanizing plant in Brazil. *Int Arch Occup Environ Health*, 73: 65-68. doi:10.1007/PL00007940 PMID:10672494
- Oller AR & Erexson G (2007). Lack of micronuclei formation in bone marrow of rats after repeated oral exposure to nickel sulfate hexahydrate. *Mutat Res*, 626: 102-110. PMID:17052950
- Oller AR, Kirkpatrick DT, Radovsky A, Bates HK (2008). Inhalation carcinogenicity study with nickel metal powder in Wistar rats. *Toxicol Appl Pharmacol*, 233: 262-275. doi:10.1016/j.taap.2008.08.017 PMID:18822311
- Ottolenghi AD, Haseman JK, Payne WW *et al.* (1975). Inhalation studies of nickel sulfide in pulmonary carcinogenesis of rats. *J Natl Cancer Inst*, 54: 1165-1172. PMID:165308
- Oyabu T, Ogami A, Morimoto Y *et al.* (2007). Biopersistence of inhaled nickel oxide nanoparticles in rat lung. *Inhal Toxicol*, 19: Suppl 155-58. doi:10.1080/08958370701492995 PMID:17886051
- Pang D, Burges DCL, Sorahan T (1996). Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945-93. *Occup Environ Med*, 53: 714-717. doi:10.1136/oem.53.10.714 PMID:8943838
- Patierno SR, Dirscherl LA, Xu J (1993). Transformation of rat tracheal epithelial cells to immortal growth variants by particulate and soluble nickel compounds. *Mutat Res*, 300: 179-193. doi:10.1016/0165-1218(93)90049-J PMID:7687017
- Poirier LA, Theiss JC, Arnold LJ, Shimkin MB (1984). Inhibition by magnesium and calcium acetates of lead subacetate- and nickel acetate-induced lung tumors in strain A mice. *Cancer Res*, 44: 1520-1522. PMID:6704965
- Pool-Zobel BL, Lotzmann N, Knoll M *et al.* (1994). Detection of genotoxic effects in human gastric and nasal mucosa cells isolated from biopsy samples. *Environ Mol Mutagen*, 24: 23-45. doi:10.1002/em.2850240105 PMID:7519553
- Pott F, Blome H, Bruch J *et al.* (1990). Einstufungsvorschlag für anorganische und organische Fasern. *Arbeitsmed Sozialmed Präventivmed*, 25: 463-466.
- Pott F, Rippe RM, Roller M *et al.* (1989). *Tumours in the abdominal cavity of rats after intraperitoneal injection of nickel compounds*. In: *Proceedings of the International Conference on Heavy Metals in the Environment: 12-15 September 1989*. Vernet JP, editor. Geneva: World Health Organization, pp. 127-129.
- Pott F, Ziem U, Reiffer FJ *et al.* (1987). Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Exp Pathol*, 32: 129-152. PMID:3436395
- Refsvik T & Andreassen T (1995). Surface binding and uptake of nickel(II) in human epithelial kidney cells: modulation by ionomycin, nicardipine and metals. *Carcinogenesis*, 16: 1107-1112. doi:10.1093/carcin/16.5.1107 PMID:7767972
- Rodriguez RE, Misra M, Diwan BA *et al.* (1996). Relative susceptibilities of C57BL/6, (C57BL/6 x C3H/He) F1, and C3H/He mice to acute toxicity and carcinogenicity of nickel subsulfide. *Toxicology*, 107: 131-140. doi:10.1016/0300-483X(95)03251-A PMID:8599172
- Rydh CJ & Svärd B (2003). Impact on global metal flows arising from the use of portable rechargeable batteries. *Sci Total Environ*, 302: 167-184. doi:10.1016/S0048-9697(02)00293-0 PMID:12526907
- Salnikow K, Su W, Blagosklonny MV, Costa M (2000). Carcinogenic metals induce hypoxia-inducible factor-stimulated transcription by reactive oxygen species-independent mechanism. *Cancer Res*, 60: 3375-3378. PMID:10910041
- Salnikow K & Zhitkovich A (2008). Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. *Chem Res Toxicol*, 21: 28-44. doi:10.1021/tx700198a PMID:17970581
- Schwerdtle T & Hartwig A (2006). Bioavailability and genotoxicity of soluble and particulate nickel compounds in cultured human lung cells. *Materialwiss Werkstofftech*, 37: 521-525. doi:10.1002/mawe.200600030

Nickel and nickel compounds

- Seilkop S (2002). Occupational exposures and pancreatic cancer. *Occup Environ Med*, 58: 63--64. . doi:10.1136/oem.58.1.63a PMID:11216453
- Seoane AI & Dulout FN (2001). Genotoxic ability of cadmium, chromium and nickel salts studied by kine-tochore staining in the cytokinesis-blocked micronu-cleus assay. *Mutat Res*, 490: 99-106. PMID:11342235
- Shirali P, Decaestecker AM, Marez T *et al.* (1991). Ni3S2 uptake by lung cells and its interaction with plasma membranes. *J Appl Toxicol*, 11: 279-288. doi:10.1002/jat.2550110409 PMID:1940002
- Sivulka DJ (2005). Assessment of respiratory carcino-genicity associated with exposure to metallic nickel: a review. *Regul Toxicol Pharmacol*, 43: 117-133. PMID:16129532
- Sivulka DJ & Seilkop SK (2009). Reconstruction of historical exposures in the US nickel alloy industry and the implications for carcinogenic hazard and risk assessments. *Regul Toxicol Pharmacol*, 53: 174-185. PMID:19545511
- Skaug V, Gylseth B, Reiss ALP *et al.* (1985). *Tumor induc-tion in rats after intrapleural injection of nickel subsulfide and nickel oxide*. In: *Progress in Nickel Toxicology*. Brown SS, Sunderman FWJ, editors. Oxford: Blackwell Scientific Publications, pp. 37-41.
- Smith-Sivertsen T, Tchachtchine V, Lund E *et al.* (1998). Urinary nickel excretion in populations living in the proximity of two russian nickel refineries: a Norwegian-Russian population-based study. *Environ Health Perspect*, 106: 503-511. doi:10.1289/ehp.98106503 PMID:9681979
- Snyder RD, Davis GF, Lachmann PJ (1989). Inhibition by metals of X-ray and ultraviolet-induced DNA repair in human cells. *Biol Trace Elem Res*, 21: 389-398. doi:10.1007/BF02917280 PMID:2484618
- Sobti RC & Gill RK (1989). Incidence of micronuclei and abnormalities in the head of spermatozoa caused by the salts of a heavy metal, nickel. *Cytologia (Tokyo)*, 54: 249-253.
- Sorahan T (2004). Mortality of workers at a plant manu-facturing nickel alloys, 1958-2000. *Occup Med (Lond)*, 54: 28-34. doi:10.1093/occmed/kqg127 PMID:14963251
- Sorahan T & Williams SP (2005). Mortality of workers at a nickel carbonyl refinery, 1958-2000. *Occup Environ Med*, 62: 80-85. doi:10.1136/oem.2004.014985 PMID:15657188
- Stoner GD, Shimkin MB, Troxell MC *et al.* (1976). Test for carcinogenicity of metallic compounds by the pulmo-nary tumor response in strain A mice. *Cancer Res*, 36: 1744-1747. PMID:1268831
- Stridsklev IC, Schaller K-H, Langård S (2007). Monitoring of chromium and nickel in biological fluids of grinders grinding stainless steel. *Int Arch Occup Environ Health*, 80: 450-454. doi:10.1007/s00420-006-0142-3 PMID:17051396
- Sunderman FW Jr (1983). Organ and species specificity in nickel subsulfide carcinogenesis. *Basic Life Sci*, 24: 107-127. PMID:6860261
- Sunderman FW Jr (1984). Carcinogenicity of nickel compounds in animals. *IARC Sci Publ*, 53: 127-142. PMID:6532978
- Sunderman FW, Donnelly AJ, West B, Kincaid JF (1959). Nickel poisoning. IX. Carcinogenesis in rats exposed to nickel carbonyl. *AMA Arch Ind Health*, 20: 36-41. PMID:13660518
- Sunderman FW Jr, Hopfer SM, Plowman MC, Knight JA (1990). Carcinogenesis bioassays of nickel oxides and nickel-copper oxides by intramuscular administra-tion to Fischer-344 rats. *Res Commun Chem Pathol Pharmacol*, 70: 103-113. PMID:2263758
- Sunderman FW, Kincaid JF, Donnelly AJ, West B (1957). Nickel poisoning. IV. Chronic exposure of rats to nickel carbonyl; a report after one year of observation. *AMA Arch Ind Health*, 16: 480-485. PMID:13478186
- Sunderman FW Jr, Maenza RM, Hopfer SM *et al.* (1979). Induction of renal cancers in rats by intrarenal injec-tion of nickel subsulfide. *J Environ Pathol Toxicol*, 2: 1511-1527. PMID:528855
- Sunderman FW Jr & McCully KS (1983). Carcinogenesis tests of nickel arsenides, nickel antimonide, and nickel telluride in rats. *Cancer Invest*, 1: 469-474. doi:10.3109/07357908309020271 PMID:6667417
- Sunderman FW Jr, McCully KS, Hopfer SM (1984). Association between erythrocytosis and renal cancers in rats following intrarenal injection of nickel compounds. *Carcinogenesis*, 5: 1511-1517. doi:10.1093/carcin/5.11.1511 PMID:6488475
- Thomassen Y, Nieboer E, Romanova N *et al.* (2004). Multi-component assessment of worker exposures in a copper refinery. Part 1. Environmental monitoring. *J Environ Monit*, 6: 985-991. doi:10.1039/b408464k PMID:15568048
- Tola S, Kilpiö J, Virtamo M (1979). Urinary and plasma concentrations of nickel as indicators of exposure to nickel in an electroplating shop. *J Occup Med*, 21: 184-188. PMID:438908
- Tundermann JH, Tien JK, Howson TE (2005). *Nickel and nickel alloys*. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Volume 17. (online edition)
- Uddin AN, Burns FJ, Rossman TG *et al.* (2007). Dietary chromium and nickel enhance UV-carcinogenesis in skin of hairless mice. *Toxicol Appl Pharmacol*, 221: 329-338. doi:10.1016/j.taap.2007.03.030 PMID:17499830
- Ulrich L, Sulcová M, Špaček L *et al.* (1991). Investigation of professional nickel exposure in nickel refinery workers. *Sci Total Environ*, 101: 91-96. doi:10.1016/0048-9697(91)90106-O PMID:2057775
- USGS (2008). *Nickel*. In: *2006 Minerals Yearbook*. Reston, VA: US Geological Survey.

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- Waalkes MP, Liu J, Kasprzak KS, Diwan BA (2004). Minimal influence of metallothionein over-expression on nickel carcinogenesis in mice. *Toxicol Lett*, 153: 357–364. doi:10.1016/j.toxlet.2004.06.003 PMID:15454311
- Waalkes MP, Liu J, Kasprzak KS, Diwan BA (2005). Metallothionein-I/II double knockout mice are no more sensitive to the carcinogenic effects of nickel subsulfide than wild-type mice. *Int J Toxicol*, 24: 215–220. doi:10.1080/10915810591000668 PMID:16126615
- Wang P, Guliaev AB, Hang B (2006). Metal inhibition of human N-methylpurine-DNA glycosylase activity in base excision repair. *Toxicol Lett*, 166: 237–247. doi:10.1016/j.toxlet.2006.06.647 PMID:16938414
- WHO (2007). Nickel in Drinking Water. WHO/SDE/WSH/07.08/55. Geneva: World Health Organization
- Woźniak K & Błasiak J (2002). Free radicals-mediated induction of oxidized DNA bases and DNA-protein cross-links by nickel chloride. *Mutat Res*, 514: 233–243. PMID:11815261
- Woźniak K & Błasiak J (2004). Nickel impairs the repair of UV- and MNNG-damaged DNA. *Cell Mol Biol Lett*, 9: 83–94. PMID:15048153
- Yarita T & Nettesheim P (1978). Carcinogenicity of nickel subsulfide for respiratory tract mucosa. *Cancer Res*, 38: 3140–3145. PMID:688205
- Zhang Q, Salnikow K, Kluz T *et al.* (2003). Inhibition and reversal of nickel-induced transformation by the histone deacetylase inhibitor trichostatin A. *Toxicol Appl Pharmacol*, 192: 201–211. doi:10.1016/S0041-008X(03)00280-1 PMID:14575637
- Zoroddu MA, Schinocca L, Kowalik-Jankowska T *et al.* (2002). Molecular mechanisms in nickel carcinogenesis: modeling Ni(II) binding site in histone H4. *Environ Health Perspect*, 110: Suppl 5719–723. PMID:12426119

ASBESTOS (CHRYSTILE, AMOSITE, CROCIDOLITE, TREMOLITE, ACTINOLITE, AND ANTHOPHYLLITE)

Asbestos was considered by previous IARC Working Groups in 1972, 1976, and 1987 ([IARC, 1973, 1977, 1987a](#)). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series. These include the serpentine mineral chrysotile (also known as ‘white asbestos’), and the five amphibole minerals – actinolite, amosite (also known as ‘brown asbestos’), anthophyllite, crocidolite (also known as ‘blue asbestos’), and tremolite ([IARC, 1973](#); [USGS, 2001](#)). The conclusions reached in this *Monograph* about asbestos and its carcinogenic risks apply to these six types of fibres wherever they are found, and that includes talc containing asbestiform fibres. Erionite (fibrous aluminosilicate) is evaluated in a separate *Monograph* in this volume.

Common names, Chemical Abstracts Service (CAS) Registry numbers and idealized chemical formulae for the six fibrous silicates designated as ‘asbestos’ are presented in [Table 1.1](#). Specific

chemical and physical properties are also presented.

1.2 Chemical and physical properties of the agent

The silicate tetrahedron (SiO_4) is the basic chemical unit of all silicate minerals. The number of tetrahedra in the crystal structure and how they are arranged determine how a silicate mineral is classified.

Serpentine silicates are classified as ‘sheet silicates’ because the tetrahedra are arranged to form sheets. Amphibole silicates are classified as ‘chain silicates’ because the tetrahedra are arranged to form a double chain of two rows aligned side by side. Magnesium is coordinated with the oxygen atom in serpentine silicates. In amphibole silicates, cationic elements such as aluminium, calcium, iron, magnesium, potassium, and sodium are attached to the tetrahedra. Amphiboles are distinguished from one another by their chemical composition. The chemical formulas of asbestos minerals are idealized. In

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Table 1.1 Common names, CAS numbers, synonyms, non-asbestos mineral analogues, idealized chemical formulae, selected physical and chemical properties of asbestos minerals

Common Name	CAS No.	Synonyms	Non-Asbestos Mineral Analogue	Idealized Chemical Formula	Colour	Decomposition Temperature (°C)	Other Properties
Asbestos	1332-21-4*	Unspecified		Unspecified			
<i>Serpentine group of minerals</i>							
Chrysotile	12001-29-5*	Serpentine asbestos; white asbestos	Lizardite, antigorite	$[\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4]_n$	White, grey, green, yellowish	600–850	Curled sheet silicate, hollow central core; fibre bundle lengths = several mm to more than 10 cm; fibres more flexible than amphiboles; net positive surface charge; forms a stable suspension in water; fibres degrade in dilute acids
<i>Amphibole group of minerals</i>							
Crocidolite	12001-28-4*	Blue asbestos	Riebeckite	$[\text{NaFe}^{2+}_3\text{Fe}^{3+}_2\text{Si}_8\text{O}_{22}(\text{OH})_2]_n$	Lavender, blue green	400–900	Double chain silicate; shorter, thinner fibres than other amphiboles, but not as thin as chrysotile; fibre flexibility: fair to good; spinnability: fair; resistance to acids: good; less heat resistance than other asbestos fibres; usually contains organic impurities, including low levels of PAHs; negative surface charge in water
Amosite	12172-73-5*	Brown asbestos	Grunerite	$[(\text{Mg}, \text{Fe}^{2+})_7\text{Si}_8\text{O}_{22}(\text{OH})_2]_n$	Brown, grey, greenish	600–900	Double chain silicate; long, straight, coarse fibres; fibre flexibility: somewhat; resistance to acids: somewhat; occurs with more iron than magnesium; negative surface charge in water
Anthophyllite	17068-78-9*	Ferroanthophyllite; azbolen asbestos	Anthophyllite	$[(\text{Mg}, \text{Fe}^{2+})_7\text{Si}_8\text{O}_{22}(\text{OH})_2]_n$	Grey, white, brown-grey, green	NR	Double chain silicate; short, very brittle fibres; resistance to acids: very; relatively rare; occasionally occurs as contaminant in talc deposits; negative surface charge in water
Actinolite	12172-67-7*	Unspecified	Actinolite	$[\text{Ca}_2(\text{Mg}, \text{Fe}^{2+})_5\text{Si}_8\text{O}_{22}(\text{OH})_2]_n$	Green	NR	Double chain silicate; brittle fibres; resistance to acids: none; occurs in asbestiform and non-asbestiform habit; iron-substituted derivative of tremolite; common contaminant in amosite deposits; negative surface charge in water
Tremolite	14567-73-8*	Silicic acid; calcium magnesium salt (8:4)	Tremolite	$[\text{Ca}_2\text{Mg}_5\text{Si}_8\text{O}_{22}(\text{OH})_2]_n$	White to pale green	950–1040	Double chain silicate; brittle fibres; acid resistant; occurs in asbestiform and non-asbestiform habit; common contaminant in chrysotile and talc deposits; negative surface charge in water

* identified as asbestos by CAS Registry
NR, not reported

From [ATSDR \(2001\)](#), [USGS \(2001\)](#), [HSE \(2005\)](#), [NTP \(2005\)](#)

natural samples, the composition varies with respect to major and trace elements ([USGS, 2001](#); [HSE, 2005](#)). More detailed information on the chemical and physical characteristics of asbestos – including atomic structure, crystal polytypes, fibre structure, chemistry and impurities – can be found in the previous *IARC Monograph* ([IARC, 1973](#)).

The structure of silicate minerals may be fibrous or non-fibrous. The terms ‘asbestos’ or ‘asbestiform minerals’ refer only to those silicate minerals that occur in polyfilamentous bundles, and that are composed of extremely flexible fibres with a relatively small diameter and a large length. These fibre bundles have splaying ends, and the fibres are easily separated from one another ([USGS, 2001](#); [HSE, 2005](#)). Asbestos minerals with crystals that grow in two or three dimensions and that cleave into fragments, rather than breaking into fibrils, are classified as silicate minerals with a ‘non-asbestiform’ habit. These minerals may have the same chemical formula as the ‘asbestiform’ variety. ([NIOSH, 2008](#)).

Chrysotile, lizardite, and antigorite are the three principal serpentine silicate minerals. Of these, only chrysotile occurs in the asbestiform habit. Of the amphibole silicate minerals, amosite and crocidolite occur only in the asbestiform habit, while tremolite, actinolite and anthophyllite occur in both asbestiform and non-asbestiform habits ([USGS, 2001](#); [HSE, 2005](#); [NTP, 2005](#)).

Historically, there has been a lack of consistency in asbestos nomenclature. This frequently contributed to uncertainty in the specific identification of asbestos minerals reported in the literature. The International Mineralogical Association (IMA) unified the current mineralogical nomenclature under a single system in 1978. This system was subsequently modified in 1997 ([NIOSH, 2008](#)).

Asbestos fibres tend to possess good strength properties (e.g. high tensile strength, wear and friction characteristics); flexibility (e.g. the ability to be woven); excellent thermal properties (e.g.

heat stability; thermal, electrical and acoustic insulation); adsorption capacity; and, resistance to chemical, thermal and biological degradation ([USGS, 2001](#); [NTP, 2005](#)).

1.3 Use of the agent

Asbestos has been used intermittently in small amounts for thousands of years. Modern industrial use dates from about 1880, when the Quebec chrysotile fields began to be exploited. During the next 50 years gradual increases in production and use were reported with a cumulative total of somewhat less than 5000 million kg mined by 1930 ([IARC, 1973](#)).

As described above, asbestos has several chemical and physical properties that make it desirable for a wide range of industrial applications. By the time industrial and commercial use of asbestos peaked, more than 3000 applications or types of products were listed ([NTP, 2005](#)). Production and consumption of asbestos has declined in recent years due to the introduction of strict regulations governing exposure and/or outright bans on exposure.

Asbestos is used as a loose fibrous mixture, bonded with other materials (e.g. Portland cement, plastics and resins), or woven as a textile ([ATSDR, 2001](#)). The range of applications in which asbestos has been used includes: roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials (e.g. brake pads and shoes), coating and compounds, plastics, textiles, paper, mastics, thread, fibre jointing, and millboard ([USGS, 2001](#); [NTP, 2005](#); [Virta, 2006](#)). Certain fibre characteristics, such as length and strength, are used to determine the most appropriate application. For example, longer fibres tend to be used in the production of textiles, electrical insulation, and filters; medium-length fibres are used in the production of asbestos cement pipes and sheets, friction materials (e.g. clutch facings, brake linings), gaskets, and pipe coverings; and,

short fibres are used to reinforce plastics, floor tiles, coatings and compounds, and roofing felts ([NTP, 2005](#)).

Since peaking in the 1970s, there has been a general decline in world production and consumption of asbestos. Peak world production was estimated to be 5.09 million metric tons in 1975, with approximately 25 countries producing asbestos and 85 countries manufacturing asbestos products ([USGS, 2001](#); [Nishikawa et al., 2008](#)). Worldwide ‘apparent consumption’ of asbestos (calculated as production plus imports minus exports) peaked at 4.73 million metric tons in 1980. Asbestos cement products are estimated to have accounted for 66% of world consumption in that year ([Virta, 2006](#)). In the USA, consumption of asbestos peaked in 1973 at 719000 metric tons ([USGS, 2001](#)).

Historical trends worldwide in per capita asbestos use are presented in [Table 1.2](#), and peak use of asbestos was higher and occurred earlier in the countries of Northern and western Europe, Oceania, and the Americas (excluding South America). Very high asbestos use was recorded in Australia (5.1 kg per capita/year in the 1970s), Canada (4.4 kg per capita/year in the 1970s), and several countries of Northern and western Europe (Denmark: 4.8 kg per capita/year in the 1960s; Germany: 4.4 kg per capita/year in the 1970s; and Luxembourg: 5.5 kg per capita/year in the 1960s) ([Nishikawa et al., 2008](#)).

Current use of asbestos varies widely. While some countries have imposed strict regulations to limit exposure and others have adopted bans, some have intervened less, and continue to use varying quantities of asbestos ([Table 1.2](#)). According to recent estimates by the US Geological Survey, world production of asbestos in 2007 was 2.20 million metric tonnes, slightly increased from 2.18 million metric ton in 2006. Six countries accounted for 96% of world production in 2006: the Russian Federation (925000 metric tons), the People’s Republic of China (360000 metric tons), Kazakhstan

(300000 metric tons), Brazil (227304 metric tons), Canada (185000 metric tons), and Zimbabwe (100000 metric tons) ([Virta, 2008](#)). During 2000–03, asbestos consumption increased in China, India, Kazakhstan, and the Ukraine ([Virta, 2006](#)). ‘Apparent’ world consumption of asbestos was 2.11 million metric tons in 2003, with the Russian Federation, several former Russian states and countries in Asia being the predominant users ([Virta, 2006](#)). Consumption of asbestos in the USA (predominantly chrysotile) was 2230 metric tons in 2006, declining to 1730 metric tons in 2007 ([Virta, 2008](#)). Roofing products (includes coatings and compounds) accounted for over 80% of asbestos consumption in the USA ([Virta, 2008](#); [Virta, 2009](#)). Asbestos products were banned in all the countries of the European Union, including Member States of eastern Europe, effective January 1, 2005 ([EU, 1999](#)).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Asbestos minerals are widespread in the environment, and are found in many areas where the original rock mass has undergone metamorphism ([ATSDR, 2001](#); [USGS, 2001](#)). Examples include large chrysotile deposits in the Ural Mountains in the Russian Federation, in the Appalachian Mountains in the USA, and in Canada ([Virta, 2006](#)). They may occur in large natural deposits or as contaminants in other minerals (e.g. tremolite asbestos may occur in deposits of chrysotile, vermiculite, and talc). The most commonly occurring form of asbestos is chrysotile, and its fibres are found as veins in serpentine rock formations. Asbestiform amphiboles occur in relatively low quantities throughout the earth’s crust and their chemical composition reflects the environment in which they form ([Virta, 2002](#)). Although most commercial deposits typically contain 5–6% of asbestos, a few deposits, such

Table 1.2 Historical trend in asbestos use per capita and status of national ban

Use of asbestos ^a (kg per capita/year)							
Country	1950s	1960s	1970s	1980s	1990s	2000s	National ban ^b
Asia							
Israel	3.13	2.87	1.23	0.78	0.44	0.02	No ban
Japan	0.56	2.02	2.92	2.66	1.81	0.46	2004
Others ^c (<i>n</i> = 39)	0.06	0.15	0.25	0.27	0.30	0.31	3/39
Eastern Europe and Southern Europe							
Croatia	0.39	1.13	2.56	2.36	0.95	0.65	No ban
Czech Republic	1.62	2.36	2.91	2.73	1.30	0.14	2005
Hungary	0.76	1.23	2.87	3.29	1.50	0.16	2005
Poland	0.36	1.24	2.36	2.09	1.05	0.01	1997
Romania	ND	ND	1.08	0.19	0.52	0.55	2007
Spain	0.32	1.37	2.23	1.26	0.80	0.18	2002
Others ^c (<i>n</i> = 15)	0.79	1.57	2.35	2.05	2.35	1.72	5/15
Northern Europe and Western Europe							
Austria	1.16	3.19	3.92	2.08	0.36	0.00	1990
Denmark	3.07	4.80	4.42	1.62	0.09	NA	1986
Finland	2.16	2.26	1.89	0.78	ND	0	1992
France	1.38	2.41	2.64	1.53	0.73	0.00	1996
Germany	1.84	2.60	4.44	2.43	0.10	0.00	1993
Iceland	0.21	2.62	1.70	0.02	0	0.00	1983
Lithuania	ND	ND	ND	ND	0.54	0.06	2005
Luxembourg	4.02	5.54	5.30	3.23	1.61	0.00	2002
Netherlands	1.29	1.70	1.82	0.72	0.21	0.00	1994
Norway	1.38	2.00	1.16	0.03	0	0.00	1984
Sweden	1.85	2.30	1.44	0.11	0.04	NA	1986
United Kingdom	2.62	2.90	2.27	0.87	0.18	0.00	1999
Others ^c (<i>n</i> = 5)	3.05	4.32	4.05	2.40	0.93	0.05	5/5

as the Coalinga chrysotile deposits in California, USA, are reported to contain 50% or more ([USGS, 2001](#); [Virta, 2006](#)).

1.4.2 Air

Asbestos is not volatile; however, fibres can be emitted to the atmosphere from both natural and anthropogenic sources. The weathering of asbestos-bearing rocks is the primary natural source of atmospheric asbestos. No estimates of the amounts of asbestos released to the air from natural sources are available ([ATSDR, 2001](#)). Anthropogenic activities are the predominant source of atmospheric asbestos fibres.

Major anthropogenic sources include: open-pit mining operations (particularly drilling and blasting); crushing, screening, and milling of the ore; manufacturing asbestos products; use of asbestos-containing materials (such as clutches and brakes on cars and trucks); transport and disposal of wastes containing asbestos; and, demolition of buildings constructed with asbestos-containing products, such as insulation, fireproofing, ceiling and floor tiles, roof shingles, drywall, and cement ([ATSDR, 2001](#); [NTP, 2005](#)). Concentrations of asbestos vary on a site-by-site basis and, as a result, environmental emissions are not easily estimated ([ATSDR, 2001](#)).

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Table 1.2 (continued)

Use of asbestos ^a (kg per capita/year)							
Country	1950s	1960s	1970s	1980s	1990s	2000s	National ban ^b
<i>Americas, excluding South America</i>							
Canada	2.76	3.46	4.37	2.74	1.96	0.32	No ban
Cuba	ND	ND	ND	0.15	0.36	0.74	No ban
Mexico	0.28	0.57	0.97	0.77	0.39	0.26	No ban
USA	3.82	3.32	2.40	0.77	0.08	0.01	No ban
Others ^c (<i>n</i> = 12)	0.06	0.22	0.44	0.29	0.07	0.07	0/12
<i>South America</i>							
Argentina	ND	0.88	0.76	0.40	0.18	0.04	2001
Brazil	0.27	0.38	0.99	1.25	1.07	0.74	2001
Chile	0.07	0.92	0.56	0.64	0.55	0.03	2001
Ecuador	ND	ND	0.67	0.52	0.14	0.26	No ban
Uruguay	ND	0.74	0.75	0.54	0.47	0.08	2002
Others ^c (<i>n</i> = 6)	0.27	0.43	0.60	0.47	0.29	0.19	0/6
<i>Oceania</i>							
Australia	3.24	4.84	5.11	1.82	0.09	0.03	2003
New Zealand	2.05	2.56	2.90	1.00	ND	ND	No ban
Others ^c (<i>n</i> = 3)	ND	ND	ND	ND	ND	0.22	0/3

^a Numbers corresponding to use of asbestos by country and region were calculated as annual use per capita averaged over the respective decade.

^b Year first achieved or year planned to achieve ban. When shown as fraction, the numerator is the number of countries that achieved bans and the denominator is the number of other countries in the region.

^c Data on asbestos use were available (but mortality data unavailable) for others in each region, in which case data were aggregated.

ND, no data available; NA, not applicable because of negative use data; 0.00 when the calculated data were < 0.005; 0 if there are no data after the year the ban was introduced.

From [Nishikawa et al. \(2008\)](#)

1.4.3 Water

Asbestos can enter the aquatic environment from both natural and anthropogenic sources, and has been measured in both ground- and surface-water samples. Erosion of asbestos-bearing rock is the principal natural source. Anthropogenic sources include: erosion of waste piles containing asbestos, corrosion of asbestos-cement pipes, disintegration of asbestos-containing roofing materials, and, industrial wastewater run-off ([ATSDR, 2001](#)).

1.4.4 Soil

Asbestos can enter the soil and sediment through natural (e.g. weathering and erosion of asbestos-bearing rocks) and anthropogenic (e.g.

disposal of asbestos-containing wastes in landfills) sources. The practice of disposing asbestos-containing materials in landfills was more common in the past, and is restricted in many countries by regulation or legislation ([ATSDR, 2001](#)).

1.4.5 Environmental releases

According to the US EPA Toxics Release Inventory, total releases of friable asbestos to the environment (includes air, water, and soil) in 1999 were 13.6 million pounds from 86 facilities that reported producing, processing, or using asbestos ([ATSDR, 2001](#)). In 2009, total releases of 8.9 million pounds of friable asbestos were reported by 38 facilities ([US EPA, 2010](#)).

1.5 Human exposure

Inhalation and ingestion are the primary routes of exposure to asbestos. Dermal contact is not considered a primary source, although it may lead to secondary exposure to fibres, via ingestion or inhalation. The degree of penetration in the lungs is determined by the fibre diameter, with thin fibres having the greatest potential for deep lung deposition ([NTP, 2005](#)).

1.5.1 Exposure of the general population

Inhalation of asbestos fibres from outdoor air, and to a lesser degree in indoor air, is the primary route of exposure for the non-smoking general population. Exposure may also occur via ingestion of drinking-water, which has been contaminated with asbestos through erosion of natural deposits, erosion of asbestos-containing waste sites, corrosion of asbestos-containing cement pipes, or filtering through asbestos-containing filters. Families of asbestos-workers may be exposed via contact with fibres carried home on hair or on clothing.

In studies of asbestos concentrations in outdoor air, chrysotile is the predominant fibre detected. Low levels of asbestos have been measured in outdoor air in rural locations (typical concentration, 10 fibres/m³ [f/m³]). Typical concentrations are about 10-fold higher in urban locations and about 1000 times higher in close proximity to industrial sources of exposure (e.g. asbestos mine or factory, demolition site, or improperly protected asbestos-containing waste site) ([ATSDR, 2001](#)). Asbestos fibres (mainly chrysotile) were measured in air and in settled dust samples obtained in New York City following destruction of the World Trade Center on September 11, 2001 ([Landrigan et al., 2004](#)).

In indoor air (e.g. in homes, schools, and other buildings), measured concentrations of asbestos are in the range of 30–6000 f/m³. Measured concentrations vary depending on the

application in which the asbestos was used (e.g. insulation versus ceiling or floor tiles), and on the condition of the asbestos-containing materials (i.e. good condition versus deteriorated and easily friable) ([ATSDR, 2001](#)).

1.5.2 Occupational exposure

Asbestos has been in widespread commercial use for over 100 years ([USGS, 2001](#)). Globally, each year, an estimated 125 million people are occupationally exposed to asbestos ([WHO, 2006](#)). Exposure by inhalation, and to a lesser extent ingestion, occurs in the mining and milling of asbestos (or other minerals contaminated with asbestos), the manufacturing or use of products containing asbestos, construction, automotive industry, the asbestos-abatement industry (including the transport and disposal of asbestos-containing wastes).

Estimates of the number of workers potentially exposed to asbestos in the USA have been reported by the National Institute of Occupational Safety and Health (NIOSH), by the Occupational Safety and Health Administration (OSHA), and the Mine Safety and Health Administration (MSHA). OSHA estimated in 1990 that about 568000 workers in production and services industries and 114000 in construction industries may have been exposed to asbestos in the workplace ([OSHA, 1990](#)). Based on mine employment data from 2002, NIOSH estimated that 44000 miners and other mine workers may have been exposed to asbestos during the mining of asbestos and some mineral commodities in which asbestos may have been a potential contaminant ([NIOSH, 2002b](#)). More recently, OSHA has estimated that 1.3 million employees in construction and general industry face significant asbestos exposure on the job ([OSHA, 2008](#)). In addition to evidence from OSHA and MSHA that indicate a reduction in occupational exposures in the USA over the past several decades, other information compiled on workplace exposures to asbestos

indicates that the nature of occupational exposures to asbestos has changed ([Rice & Heineman, 2003](#)). Once dominated by chronic exposures in manufacturing process such as textile mills, friction-product manufacturing, and cement-pipe fabrication, current occupational exposures to asbestos primarily occur during maintenance activities or remediation of buildings that contain asbestos.

In Europe, estimates of the number of workers exposed to asbestos have been developed by CAREX (CARcinogen EXposure). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that a total of 1.2 million workers were exposed to asbestos in 41 industries in the 15 Member States of the EU. Over 96% of these workers were employed in the following 15 industries: ‘construction’ ($n = 574000$), ‘personal and household services’ ($n = 99000$), ‘other mining’ ($n = 85000$), ‘agriculture’ ($n = 81000$), ‘wholesale and retail trade and restaurants and hotels’ ($n = 70000$), ‘food manufacturing’ ($n = 45000$), ‘land transport’ ($n = 39000$), ‘manufacture of industrial chemicals’ ($n = 33000$), ‘fishing’ ($n = 25000$), ‘electricity, gas and steam’ ($n = 23000$), ‘water transport’ ($n = 21000$), ‘manufacture of other chemical products’ ($n = 19000$), ‘manufacture of transport equipment’ ($n = 17000$), ‘sanitary and similar services’ ($n = 16000$), and ‘manufacture of machinery, except electrical’ ($n = 12000$). Despite the total ban of asbestos, about 1500 workers (mainly construction workers and auto mechanics) were reported as having exposure to asbestos on the Finnish Register of Workers Exposed to Carcinogens (ASA Register) in 2006 ([Saalo et al., 2006](#)). In 2004, approximately 61000 workers performing demolition and reconstruction work in Germany were registered in the Central Registration Agency for Employees Exposed to Asbestos Dust ([Hagemeyer et al., 2006](#)).

Exposure to asbestos in occupational settings is regulated in countries of the EU. According to the European Directive of the EC 2003/18, permissible limits are 0.1 [f/mL] for all types of asbestos, based on an 8-hour time-weighted average (8h-TWA) ([EU, 2003](#)). The same limit is in force in most Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, Newfoundland and Labrador, Prince Edward Island, New Brunswick and Nova Scotia); New Zealand; Norway; and, the USA. Other countries have permissible limits of up to 2 fibres/cm³ ([ACGIH, 2007](#)).

Since 1986, the annual geometric means of occupational exposure concentrations to asbestos reported in the OSHA database and the MSHA database have been consistently below the NIOSH recommended exposure limit (REL) of 0.1 f/mL for all major industry divisions in the USA. The number of occupational asbestos exposure samples that were measured and reported by OSHA decreased from an average of 890 per year during 1987–94 to 241 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 6.3% during 1987–1994 to 0.9% during 1995–99. During the same two periods, the number of exposures measured and reported in the MSHA database decreased from an average of 47 per year during 1987–94 to an average of 23 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 11.1% during 1987–94 to 2.6% during 1995–99 ([NIOSH, 2002a](#)).

Data from studies and reviews of occupational asbestos exposure published since the previous *IARC Monograph* ([IARC, 1973](#)) are summarized below.

(a) *Studies of occupational exposure*

In a mortality study of 328 employees of an asbestos-cement factory in Ontario, Canada, [Finkelstein \(1983\)](#) constructed an exposure model on the basis of available air sampling data, and calculated individual exposure histories to

investigate exposure–response relationships for asbestos-associated malignancies. In retrospectively estimating exposure, the following assumptions were made: exposures did not change during 1962–70, exposures during 1955–61 were 30% higher than the later period, and exposures during 1948–54 were twice as high as during 1962–70. Exposure estimates for the years 1949, 1969, and 1979 were as follows: 40, 20, 0.2 f/mL for the willows operators; 16, 8, 0.5 f/mL for the forming machine operators; and, 8, 4, 0.3 f/mL for the lathe operators.

In an occupational hygiene survey of 24 Finnish workplaces, asbestos concentrations were measured during the different operations of brake maintenance of passenger cars, trucks and buses. During brake repair of trucks or buses, the estimated 8-hour time-weighted average exposure to asbestos was 0.1–0.2 [f/mL]. High levels of exposure (range, 0.3–125 [f/mL]; mean, 56 [f/mL]) were observed during brake maintenance if local exhaust ventilation was not used. Other operations in which the concentration exceeded 1 [f/mL] included cleaning of brakes with a brush, wet cloth or compressed air jet without local exhaust ([Kauppinen & Korhonen, 1987](#)).

[Kimura \(1987\)](#), in Japan, reported the following geometric mean concentrations: bag opening and mixing, 4.5–9.5 f/mL in 1970–75 and 0.03–1.6 f/mL in 1984–86; cement cutting and grinding, 2.5–3.5 f/mL in 1970–75 and 0.17–0.57 f/mL in 1984–86; spinning and grinding of friction products, 10.2–35.5 f/mL in 1970–75 and 0.24–5.5 f/mL in 1984–86.

[Albin *et al.* \(1990\)](#) examined total and cause-specific mortality among 1929 Swedish asbestos cement workers employed at a plant producing various products (e.g. sheets, shingles, ventilation pipes) from chrysotile and, to a lesser extent, crocidolite and amosite asbestos. Individual exposures were estimated using dust measurements available for the period 1956–77. Levels of exposure were estimated for the following operations: milling, mixing, machine line, sawing, and

grinding. Asbestos concentrations ranged from 1.5–6.3 f/mL in 1956, to 0.3–5.0 f/mL in 1969, and to 0.9–1.7 f/mL in 1975. In all three time periods, the highest concentrations were observed in the milling and grinding operations.

The [Health Effects Institute \(1991\)](#) evaluated an operation and maintenance programme in a hospital on the basis of 394 air samples obtained during 106 on-site activities. The mean asbestos concentration was approximately 0.11 f/mL for personal samples, and approximately 0.012 f/mL for area samples. Eight-hour TWA concentrations showed that 99% of the personal samples were below 0.2 f/mL, and 95% below 0.1 f/mL.

[Price *et al.* \(1992\)](#) estimated the TWAs of asbestos exposures experienced by maintenance personnel on the basis of 1227 air samples collected to measure airborne asbestos levels in buildings with asbestos-containing materials. TWA exposures were 0.009 f/mL for telecommunication switch work, 0.037 f/mL for above-ceiling maintenance work, and 0.51 f/mL for work in utility spaces. Median concentrations were in the range of 0.01–0.02 f/mL.

[Weiner *et al.* \(1994\)](#) reported concentrations in a South African workshop in which chrysotile asbestos cement sheets were cut into components for insulation. The sheets were cut manually, sanded and subsequently assembled. Initial sampling showed personal sample mean concentrations of 1.9 f/mL for assembling, 5.7 f/mL for sweeping, 8.6 f/mL for drilling, and 27.5 f/mL for sanding. After improvements and clean-up of the work environment, the concentrations fell to 0.5–1.7 f/mL.

In a 1985 study, [Higashi *et al.* \(1994\)](#) collected personal and area samples at two manufacturing and processing locations in five Japanese plants manufacturing asbestos-containing products (a roofing material plant; a plant making asbestos cement sheets; a friction-material plant; and two construction and roofing-material plants). Geometric average concentrations of 0.05–0.45

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f/mL were measured in area samples, and 0.05–0.78 f/mL in personal samples.

To assess the contribution of occupational asbestos exposure to the occurrence of mesothelioma and lung cancer in Europe, [Albin *et al.* \(1999\)](#) reviewed and summarized the available information on asbestos consumption in Europe, the proportion of the population exposed and levels of exposure. Ranges of exposure were reported for the former Yugoslavia, Poland, and Latvia. In 1987, mean fibre concentrations in Serbia and Montenegro were 2–16 f/mL for textile manufacturing, 3–4 f/mL for friction materials production, and 1–4 f/mL for asbestos cement production. In Poland, exposure levels in 1994 were estimated to be much greater than 2 f/mL in the textile industry, approximately 2 f/mL in asbestos cement and friction-products manufacturing, and greater than 0.5 f/mL in downstream use. In the Latvian asbestos cement industry in 1994, ranges of fibre concentrations were 0.1–1.1 f/mL for the machine line, and 1.1–5.2 f/mL for the milling and mixing areas.

Since 1974, NIOSH has conducted a series of sampling surveys in the USA to gather information on exposure of brake mechanics to airborne asbestos during brake repair. These surveys indicated that the TWA asbestos concentrations (about 1–6 hours in duration) during brake servicing were in the range of 0.004–0.28 f/mL, and the mean TWA concentration, approximately 0.05 f/mL ([Paustenbach *et al.*, 2004](#)).

Based on a review of the historical literature on asbestos exposure before 1972 and an analysis of more than 26000 measurements collected during 1972–90, [Hagemeyer *et al.* \(2006\)](#) observed a continual decrease in workplace levels of airborne asbestos from the 1950s to 1990 in Western Germany (FRG) and Eastern Germany (GDR). High concentrations of asbestos fibres were measured for some working processes in Western Germany (e.g. asbestos spraying (400 [f/mL]), removal of asbestos insulations in the ship repair industry (320 [f/mL]), removal of asbestos

insulation (300 [f/mL]), and cutting corrugated asbestos sheets (60 [f/mL]), see [Table 1.3](#).

In a study at a large petroleum refinery in Texas, USA, [Williams *et al.* \(2007a\)](#) estimated 8h-TWA asbestos exposures for 12 different occupations (insulators, pipefitters, boiler-makers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, laborers, and maintenance workers) from the 1940s to the 1985 onwards. Estimates were calculated using information on the historical use of asbestos, the potential for exposure due to daily work activities, occupational hygiene sampling data, historical information on task-specific exposures, and use of personal protective equipment. Exposures were estimated for 1940–50, 1951–65, 1966–71, 1972–75, 1976–85, and 1985 onwards. For these time periods, the 8h-TWA exposure (50th percentile) estimates for insulators were, respectively, 9 f/mL, 8 f/mL, 2 f/mL, 0.3 f/mL, 0.005 f/mL, and < 0.001 f/mL. For all other occupations, with the exception of labourers, estimated 8h-TWA exposure estimates were at least 50- to 100-fold less than that of insulators. Estimated 8h-TWA exposure estimates for labourers were approximately one-fifth to one-tenth of those of insulators.

[Williams *et al.* \(2007b\)](#) reviewed historical asbestos exposures (1940–2006) in various non-shipyard and shipyard settings for the following skilled occupations: insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, labourers, maintenance workers, and abatement workers. For activities performed by insulators in various non-shipyard settings from the late 1960s and early 1970s, average task-specific and/or full-shift airborne fibre concentrations ranged from about 2 to 10 f/mL. Average fibre concentrations in US shipyards were about 2-fold greater, and excessively high concentrations (attributed to the spraying of asbestos) were reported in some British Naval shipyards. The introduction of improved occupational hygiene

Table 1.3 Examples of asbestos fibre concentrations in the air (f/cm³) of different workplaces in Germany

Work area		1950–54 ^a	1970–74	1980	1990
Textile industries	FRG	100	10	3.8	0.9
	GDR	100	12	6.2	2.2
Production of gaskets	FRG	60	6.6	4.7	0.7
	GDR	60	8.0	7.8	1.6
Production of cement	FRG	200	11	1.1	0.3
	GDR	200	13	1.9	0.7
Production of brake pads	FRG	150	9.1	1.4	0.7
	GDR	150	11	2.4	1.6
Insulation works	FRG	15	15	8.6	0.2
	GDR	18	18	14.0	0.5

^a Data for the GDR before 1967 are extrapolated

FRG, Federal Republic of Germany; GDR, German Democratic Republic

From [Hagemeyer et al. \(2006\)](#)

practices resulted in a 2- to 5-fold reduction in average fibre concentrations for insulator tasks. The typical range of average fibre concentration for most other occupations was < 0.01–1 f/mL. Concentrations varied with task and time period, with higher concentrations observed for tasks involving the use of powered tools, the mixing or sanding of drywall cement, and the cleanup of asbestos insulation or lagging materials. It was not possible with the available data to determine whether the airborne fibres were serpentine or amphibole asbestos.

[Madl et al. \(2007\)](#) examined seven simulation studies and four work-site industrial hygiene studies to estimate the concentration of asbestos fibres to which workers may have historically been exposed while working with asbestos-containing gaskets and packing materials in specific industrial and maritime settings (e.g. refinery, chemical, ship/shipyard). These studies involved the collection of more than 300 air samples and evaluated specific activities, such as the removal and installation of gaskets and packings, flange cleaning, and gasket formation. In all but one of the studies, the short-term average exposures were less than 1 f/mL, and all of the long-term average exposures were less than 0.1

f/mL. Higher short-term average concentrations were observed during the use of powered tools versus hand-held manual tools during gasket formation (0.44 f/mL versus 0.1 f/mL, respectively). Peak concentrations of 0.14 f/mL and 0.40 f/mL were observed during ‘gasket removal and flange face cleaning with hand tools’ and ‘packing removal and installation’, respectively.

(b) Dietary exposure

The general population can be exposed to asbestos in drinking-water. Asbestos can enter potable water supplies through the erosion of natural deposits or the leaching from waste asbestos in landfills, from the deterioration of asbestos-containing cement pipes used to carry drinking-water or from the filtering of water supplies through asbestos-containing filters. In the USA, the concentration of asbestos in most drinking-water supplies is less than 1 f/mL, even in areas with asbestos deposits or with asbestos cement water supply pipes. However, in some locations, the concentration in water may be extremely high, containing 10–300 million f/L (or even higher). The average person drinks about 2 litres of water per day ([ATSDR, 2001](#)). Risks of exposure to asbestos in drinking-water

may be especially high for small children who drink seven times more water per day per kg of body weight than the average adult ([National Academy of Sciences, 1993](#)).

1.6 Talc containing asbestiform fibres

Talc particles are normally plate-like. These particles, when viewed on edge under the microscope in bulk samples or on air filters, may appear to be fibres, and have been misidentified as such. Talc may also form true mineral fibres that are asbestiform in habit. In some talc deposits, tremolite, anthophyllite, and actinolite may occur. Talc containing asbestiform fibres is a term that has been used inconsistently in the literature. In some contexts, it applies to talc containing asbestiform fibres of talc or talc intergrown on a nanoscale with other minerals, usually anthophyllite. In other contexts, the term asbestiform talc has erroneously been used for talc products that contain asbestos. Similarly, the term asbestiform talc has erroneously been used for talc products that contain elongated mineral fragments that are not asbestiform. These differences in the use of the same term must be considered when evaluating the literature on talc. For a more detailed evaluation of talc not containing asbestiform fibres, refer to the previous *IARC Monograph* ([IARC, 2010](#)).

1.6.1 Identification of the agent

Talc (CAS No. 14807-96-6) is a designation for both the mineral talc and for commercial products marketed as ‘talc’, which contain the mineral in proportions in the range of 35% to almost 100%. Commercial talc is classified as ‘industrial talc’ (refers to products containing minerals other than talc), ‘cosmetic talc’ (refers to products, such as talcum powder, which contain > 98% talc), and ‘pharmaceutical talc’ (refers to products containing > 99% talc) ([Rohl et al., 1976](#); [Zazenski et al., 1995](#)). Synonyms for talc include:

Agalite, French chalk, kerolite, snowgoose, soap-stone, steatite, talcite, and talcum.

1.6.2 Chemical and physical properties of the agent

The molecular formula of talc is $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$. It is a hydrated magnesium sheet silicate mineral, whose structure is composed of a layer of $\text{MgO}_4(\text{OH})_2$ octahedra sandwiched between identical layers of SiO_4 tetrahedra. In nature, the composition of talc varies depending on whether or not the magnesium has been substituted with other cations, such as iron, nickel, chromium or manganese ([Rohl et al., 1976](#); [IMA, 2005](#)). Pure talc is translucent, appearing white when finely ground ([Zazenski et al., 1995](#)). The colour of talc changes in the presence of substituted cations, ranging from pale-green to dark-green, brownish or greenish-grey. Talc has the following chemical and physical properties: melting point, 1500°C; hardness, 1 on the Moh’s scale of mineral hardness; density, 2.58–2.83; and cleavage, (001) perfect ([Roberts et al., 1974](#)). Talc is a very stable mineral, and is insoluble in water, weak acids and alkalis, is neither explosive nor flammable, and has very little chemical reactivity ([IMA, 2005](#)).

Talc’s structure is crystalline. It can have a small, irregular plate structure (referred to as microcrystalline talc) or it can have large, well defined platelets (referred to as macrocrystalline talc). Its platyness and crystallinity determine the specific commercial applications for which it is suitable ([Zazenski et al., 1995](#)). Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition ([Rohl et al., 1976](#)). Many talc-bearing rocks are formed from magnesia- and silica-rich ultramafic rocks. These rocks have a central core of serpentinite surrounded by successive shells of talc-abundant rock (e.g. talc carbonate and steatite). The serpentinite core is composed mostly of non-asbestiform serpentine minerals (lizardite

and antigorite); however, small amounts of chrysotile asbestos may occur. ([Zazenski et al., 1995](#)).

More detail on the chemical and physical properties of talc can be found in the previous *IARC Monograph* ([IARC, 2010](#)).

1.6.3 Use of the agent

Talc has several unique chemical and physical properties (such as platyness, softness, hydrophobicity, organophilicity, inertness) that make it desirable for a wide range of industrial and commercial applications (e.g. paint, polymers, paper, ceramics, animal feed, rubber, roofing, fertilizers, and cosmetics). In these products, talc acts as an anti-sticking and anti-caking agent, lubricant, carrier, thickener, absorbent, and strengthening and smoothing filler ([IMA, 2005](#)).

In 2000, the worldwide use pattern for talc was as follows: paper industry, 30%; ceramics manufacture, 28%; refractories, 11%; plastics, 6%; filler or pigment in paints, 5%; roofing applications, 5%; cement, 3%; cosmetics, 2%; and other miscellaneous uses, 10% (includes agriculture and food, art sculpture, asphalt filler, auto-body filler, construction caulks, flooring, and joint compounds) ([Roskill Information Services Ltd, 2003](#)). According to a Mineral Commodity Summary published by the USGS in 2009, talc produced in the USA was used for ceramics, 31%; paper, 21%; paint, 19%; roofing, 8%; plastics, 5%; rubber, 4%; cosmetics, 2%; and other, 10% ([Virta, 2009](#)).

No information on the use of asbestiform talc in various industries (apart from mining and milling of talc from deposits containing asbestiform fibres) was identified by the Working Group. For a more detailed description of the uses of talc, refer to the previous *IARC Monograph* ([IARC, 2010](#)).

1.6.4 Environmental occurrence

(a) Natural occurrence

Primary talc deposits are found in almost every continent around the world. Talc is commonly formed by the hydrothermal alteration of magnesium- and iron-rich rocks (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites ([Zazenski et al., 1995](#)). For more detailed information on the formation of commercially important talc deposits, refer to the previous *IARC Monograph* ([IARC, 2010](#)).

Talc deposits whose protoliths are ultramafic rocks (or mafic) are abundant in number but small in total production. They are found in discontinuous bodies in orogenic belts such as the Alps, the Appalachians, and the Himalayas; these types of talc deposits form during regional metamorphism accompanying orogenesis. They also occur in the USA (California, Arkansas, Texas), Germany, Norway, Canada (Ontario and Quebec), southern Spain, Finland, the Russian Federation (Shabry and Miassy), and Egypt. Chlorite and amphibole are usually associated with this type of talc deposit although they are commonly separated in space from the talc ore (Vermont). The amphiboles may or may not be asbestiform, depending on the local geological history ([IARC, 2010](#)).

Talc deposits formed from the alteration of magnesian carbonate and sandy carbonate such as dolomite and limestone are the most important in terms of world production. Two types are recognized:

- those derived from hydrothermal alteration of unmetamorphosed or minimally metamorphosed dolomite such as found in Australia (Mount Seabrook and Three Springs); USA (Wintersboro, Alabama; Yellowstone, Montana; Talc City, California; Metaline Falls, Washington; and West Texas); the Republic of Korea; the People's Republic of China; India; the

- Russian Federation (Onot); and, northern Spain (Respina)
- those derived from hydrothermal alteration (including retrograde metamorphism) of regionally metamorphosed siliceous dolomites and other magnesium-rich rocks such as in the USA (Murphy Marblebelt, North Carolina; Death Valley-Kingston Range, California; Gouverneur District, New York; Chatsworth, Georgia); Canada (Madoc); Italy (Chisone Valley); the Russian Federation (Krasnoyarsk); Germany (Wunsiedel); Austria (Leoben); Slovakia (Gemerska); Spain; France (Trimouns); and Brazil (Brumado) (IARC, 2010).

In a study to examine the amphibole asbestos content of commercial talc deposits in the USA, [Van Gosen et al. \(2004\)](#) found that the talc-forming environment (e.g. regional metamorphism, contact metamorphism, or hydrothermal processes) directly influenced the amphibole and amphibole-asbestos content of the talc deposit. Specifically, the study found that hydrothermal talcs consistently lack amphiboles as accessory minerals, but that contact metamorphic talcs show a strong tendency to contain amphiboles, and regional metamorphic talc bodies consistently contain amphiboles, which display a variety of compositions and habits (including asbestiform). Death Valley, California is an example of a contact metamorphic talc deposit that contains accessory amphibole-asbestos (namely talc-tremolite).

1.6.5 Human exposure

(a) Exposure of the general population

Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure. As talc is used as an anti-sticking

agent in several food preparations (e.g. chewing gum), ingestion may also be a potential, albeit minor, route of exposure.

As late as 1973, some talc products sold in the USA contained detectable levels of chrysotile asbestos, tremolite, or anthophyllite ([Rohl et al., 1976](#)), and it is possible that they remained on the market in some places in the world for some time after that ([Jehan, 1984](#)). Some of the tremolite and anthophyllite may have been asbestiform in habit ([Van Gosen, 2006](#)).

[Blount \(1991\)](#) examined pharmaceutical- and cosmetic-grade talcs for asbestiform amphibole content using a density-optical method. High-grade talc product samples ($n = 15$) were collected from deposits in Montana, Vermont, North Carolina, Alabama, and from outside the USA but available in the US market. Samples were uniformly low in amphibole content (with counts in the range of 0–341 particles/mg), and some samples appeared to be completely free of amphibole minerals. In samples containing amphibole minerals, cleavage-type and asbestos-type minerals were observed. Only one sample was found to contain an amphibole particle size distribution typical of asbestos.

More complete information on the levels of exposure experienced by the general population can be found in the previous *IARC Monograph* ([IARC, 2010](#)).

(b) Occupational exposure

Inhalation is the primary route of exposure to talc in occupational settings. Exposure by inhalation to talc dust occurs in the talc-producing industries (e.g. during mining, crushing, separating, bagging, and loading), and in the talc-using industries (e.g. rubber dusting and addition of talcs to ceramic clays and glazes). Because industrial talc is a mixture of various associated minerals, occupational exposure is to a mixture of mineral dusts ([IARC, 1987b](#)).

In general, data on numbers of workers occupationally exposed to talc are lacking. The

National Occupation Exposure Survey (NOES), which was conducted by the US National Institute for Occupational Safety and Health (NIOSH) during 1981–83, estimated that 1.4 million workers, including approximately 350000 female workers, were potentially exposed to talc in the workplace ([NIOSH, 1990](#)). CAREX reports that approximately 28000 workers were exposed to talc containing asbestiform fibres in the workplace within the 15 countries that comprised the EU during 1990–93; however, some major industries producing or using talc were not included.

Many of the early measurements reported very high levels of talc dust exposures in mining and milling operations, often in the range of several mg/m³, but there is evidence of decreasing exposures ([IARC, 1987b](#); [IARC, 2010](#)). For example, before the adoption of technical preventive means in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf in the mines, and approximately 25 mppcf in the mills. Exposures in both areas were reduced to less than 10 mppcf after 1965 when improved occupational hygiene practices were implemented ([Rubino et al., 1976](#)). Although the presence of asbestiform talc was often not reliably verified, it is likely that these levels have also decreased, in part due to mine closures and regulatory controls.

[Oestenstad et al. \(2002\)](#) developed a job-exposure matrix for respirable dust, covering all work areas in an industrial grade (tremolitic) talc mining and milling facility in upstate New York, USA. The facility started operating in 1948 with the opening of an underground mine (Mine 1) and a mill (Mill 1). An open pit mine (Mine 2) opened in 1974. Talc from the facility was used predominantly for manufacturing paint and ceramic tiles. The range of all respirable dust concentrations measured in the two baseline exposure surveys was 0.01–2.67 mg/m³, with an arithmetic mean of 0.47 mg/m³ and a geometric mean of 0.28 mg/m³.

Only limited information is available about exposures in secondary industries in which talc is used or processed further. The previous *IARC Monograph* on talc ([IARC, 2010](#)) summarizes three historical surveys conducted in these kinds of industries. The IARC Working Group in 1987 noted, however, that even when measurements of respirable fibres were reported, no electron microscopic analysis was conducted to confirm the identity of the fibres. Recently, most industries using talc use non-asbestiform talc ([IARC, 2010](#)).

For a more complete description of studies in which occupational exposure to talc and talc-containing products has been reported, refer to the previous *IARC Monograph* ([IARC, 2010](#)).

2. Cancer in Humans

2.1 Introduction

The previous *IARC Monographs* were limited to the same six commercial forms of asbestos fibres (chrysotile, actinolite, amosite, anthophyllite crocidolite and tremolite) that are subject of this current evaluation. In the previous *IARC Monograph* ([IARC, 1977](#)), the epidemiological evidence showed a high incidence of lung cancer among workers exposed to chrysotile, amosite, anthophyllite, and with mixed fibres containing crocidolite, and tremolite. Pleural and peritoneal mesotheliomas were reported to be associated with occupational exposures to crocidolite, amosite, and chrysotile. Gastrointestinal tract cancers were reported to have been demonstrated in groups occupationally exposed to amosite, chrysotile or mixed fibres containing chrysotile. An excess of cancer of the larynx in occupationally exposed individuals was also noted. Finally the *Monograph* points out that mesothelioma may occur among individuals living in neighbourhoods of asbestos factories

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and crocidolite mines, and in persons living with asbestos workers.

Extensive epidemiological research on asbestos has been conducted since then. The associations between asbestos exposure, lung cancer, and mesothelioma have been well established in numerous epidemiological investigations. The epidemiological evidence for other cancer sites is less extensive than it is for lung cancer and mesothelioma, but is still considerable for some. In reviewing these studies, there are some common limitations that need to be borne in mind, which may explain the heterogeneity of the findings from the studies such as:

- The types, fibre sizes and levels of asbestos exposure differed from industry to industry and over time. Most of the heaviest exposures probably occurred in the first two-thirds of the twentieth century in asbestos mining and milling, insulation work, shipyard work, construction, and asbestos textile manufacture. Workers in different industries, eras, and geographic locales were exposed to different types of asbestos fibres, and to fibres of greatly varying dimensions.
- There were differences in how the studies handle the issue of latency or in other words time since first occupational exposure to asbestos. Some studies, especially earlier investigations, accumulated person-years from first exposure, a procedure that may dilute observed risk by including many years of low risk. Others have only accumulated person-years after a certain period of time after first exposure, usually 20 years. Also different studies followed their populations for very different periods of time since first occupational exposure to asbestos.
- The most pervasive problem in interpreting studies was the wide variation among studies in the approaches taken for exposure assessment. Some studies made no

attempt to assess exposure beyond documenting employment of study participants in a trade or industry with potential for occupational exposure to asbestos. Other studies used surrogate indices of exposure such as duration of employment or self-reported intensity of exposure, or stratified subjects' exposure by job title. Some used the skills and knowledge of industrial hygienists, obtained direct measurements of asbestos dust levels in air, and developed job-exposure matrices and cumulative exposure indices. Even these analyses are limited by the fact that earlier studies used gravimetric measures of dust exposure, while later used fibre-counting methods based on phase contrast microscopy (PCM). Factors that were used to convert between gravimetric and PCM based measurements are generally unreliable unless they are based on side by side measurements taken in specific industrial operations. Differences in fibre size distributions and fibre type can only be detected using electron microscopy, which has been done in only a very few studies.

- Misclassification of disease was a serious problem for several of the cancer sites. This is particularly true for mesothelioma, which did not have diagnostic category in the ICD system until the 10th review was initiated in 1999.

There were also issues regarding the potential for misclassification of mesotheliomas as colon or ovarian cancers.

For talc that contains asbestiform fibres, previous Working Groups assessed studies on talc described as containing asbestiform tremolite and anthophyllite ([IARC, 1987a, b](#)). These fibres fit the definition of asbestos, and therefore a separate review of talc containing asbestiform fibres was not undertaken by this Working Group. The reader is invited to consult the General Remarks

in this volume for further details. For a review of Talc, refer to the previous *IARC Monograph* ([IARC, 2010](#)).

2.2 Cancer of the lung

2.2.1 Occupational exposure

Signs that cancer of the lung could be induced by exposure to asbestos was first raised by reports of lung cancer cases that occurred among workers with asbestosis ([Gloyne, 1935](#); [Lynch & Smith, 1935](#)). The first cohort study that demonstrated an excess of lung cancer among asbestos exposed workers was a study of textile workers ([Doll, 1955](#)). In this study, 11 cases of lung cancer versus 0.8 expected ($P < 0.00001$) were reported based on national mortality rates. Since 1955, an association between lung cancer and occupational exposure to asbestos has been demonstrated in numerous cohort and case-control studies that are summarized in Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.1.pdf>, Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.2.pdf>, and Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.3.pdf>.

Although a causal association between asbestos exposure and lung cancer is generally well recognized, there are still substantial controversies on how the risk might vary by exposure to different fibre types and sizes, and whether there is a risk at low levels of exposure (i.e. environmental exposures). Particularly controversial is the question of whether chrysotile asbestos is less potent for the induction of lung cancer than the amphibole forms of asbestos (e.g. crocidolite, amosite and tremolite), which has sometimes been referred to as the “amphibole hypothesis” ([Cullen, 1996](#); [Stayner et al., 1996](#); [McDonald, 1998](#)). This argument is based on the observation from experimental

studies that chrysotile asbestos is less biopersistent (i.e. has a shorter half life) in the lung than the amphiboles. Pathological studies of tissue using electron microscopy and energy dispersive analysis of X-rays (EDAX) have been used to measure the amounts of different asbestos fibre types in the lung. Case studies of Canadian chrysotile asbestos workers using these methods have shown an unexpectedly high proportion of amphibole (primarily tremolite) fibres, considering the relatively low percentage of amphibole fibres in commercial chrysotile asbestos ([Pooley, 1976](#); [Rowlands et al., 1982](#); [Addison & Davies, 1990](#)). [The Working Group noted that the lower biopersistence of chrysotile in the lung does not necessarily imply that it would be less potent than amphiboles for lung cancer.]

Several meta-analyses have been conducted in which the relative potency of different fibre types and other fibre characteristics have been considered in relation to lung cancer. [Lash et al. \(1997\)](#) conducted a meta-analysis based on the findings from 15 cohort studies with quantitative information on the relationship between asbestos exposure and lung cancer risk. The slopes of the lung cancer exposure-response relationship from these studies were analysed using fixed and random effects models. Substantial heterogeneity in the slopes for lung cancer from these studies was found in their analysis. The heterogeneity was largely explained by industry category, dose measurements, tobacco habits, and standardization procedures. There was no evidence in this meta-analysis that differences in fibre type explained the heterogeneity of the slope.

[Hodgson & Darnton \(2000\)](#) performed a meta-analysis based on 17 cohort studies with information on the average level of asbestos exposure for the cohort as a whole or for subgroups in the study. The percentage excess lung cancer risk from each study or subgroup was divided by its average exposure level to derive a slope (RL) for the analysis. Substantial heterogeneity in the findings for lung cancer was also found in this

analysis particularly for the chrysotile cohorts. The heterogeneity in the findings for the chrysotile cohorts was largely attributable to differences in the findings from the studies of chrysotile miners and millers in Quebec ([McDonald et al., 1983](#)), and asbestos textile workers in South Carolina ([Dement & Brown, 1994](#); [Hein et al., 2007](#)), which differed by nearly 100-fold. No explanation has been found for these extreme differences although several possible explanations have been investigated. Co-exposure to mineral oils in the South Carolina textile plant was proposed as a possible explanation. A nested case-control conducted with the South Carolina cohort failed to provide evidence to support the hypothesis that mineral exposure was associated with an increased risk of lung cancer in this study population ([Dement & Brown, 1994](#)). Differences in fibre size distributions have also been considered to be a potential explanation. The asbestos textile industry workers may have used a higher grade of asbestos resulting in exposures to a greater percentage of long fibres than what was experienced by miners and millers in Quebec. A larger percentage of long fibres was found in a recent reanalysis of samples from the South Carolina cohort using transmission electron microscopy (TEM) ([Dement et al., 2008](#)) than what was previously reported in TEM analyses of samples from the Quebec mines and mills ([Gibbs & Hwang, 1975, 1980](#)). Based on their analysis, [Hodgson & Darnton \(2000\)](#) concluded that the ratio between lung cancer risk for chrysotile and the amphiboles was somewhere between 1:10 and 1:50. However, in their analyses (where they excluded the study of Quebec miners rather than the South Carolina cohort), there was only a 2-fold difference in findings for lung cancer risk between the chrysotile (RL = 2.3) and amphibole cohorts (RL = 4.2). [The Working Group noted that there is no justification for exclusion of the South Carolina cohort because it is one of the highest quality studies in terms of the exposure information used in this study.]

[Berman & Crump \(2008a\)](#) published a meta-analysis that included data from 15 asbestos cohort studies. Lung cancer risk potency factors ($Kis = [RR-1]/\text{cumulative exposure}$) were derived in their analyses that were specific for both fibre type (chrysotile versus amphiboles) and fibre size (length and width). Fibre size information was only available for one of the cohort studies, and for the other studies it was obtained from studies that were conducted in similar industrial settings. As with the previous analyses, substantial variation was found in the findings from these studies with results for lung cancer varying by two orders of magnitude, although no formal statistical tests of heterogeneity were performed. The hypothesis that chrysotile is equipotent as the amphiboles for lung cancer was not rejected for fibres of all widths ($P = 0.07$) or for thick (width $> 0.2 \mu\text{m}$) fibres ($P = 0.16$). For thin fibres (width $< 0.2 \mu\text{m}$), there was significant ($P = 0.002$) evidence that chrysotile fibres were less potent than amphiboles. Sensitivity analyses were also conducted in which the South Carolina or Quebec miners and millers cohorts were dropped from the analysis using fibres of all widths. Dropping the South Carolina cohort resulted in a highly significant ($P = 0.005$) result that potency was greater for amphiboles than for chrysotile. Dropping the Quebec cohort resulted in there being no significant ($P = 0.55$) evidence of a difference in potency between the fibre types. [The Working Group noted that both the Hodgson & Darnton and Berman & Crump analyses reveal a large degree of heterogeneity in the study findings for lung cancer, and that findings are highly sensitive to the inclusion or exclusion of the studies from South Carolina or Quebec. The reasons for the heterogeneity are unknown, and until they are explained it is not possible to draw any firm conclusions concerning the relative potency of chrysotile and amphibole asbestos fibres from these analyses.]

Based on findings from experimental studies, it is suspected that long and thin fibres are likely

to be more potent than short and thick fibres in the induction of lung cancer in humans. Unfortunately until recently, all of the epidemiological studies that have been conducted used methods for exposure assessment that did not include a determination of fibre size, and thus this issue could not be directly addressed with these studies. As described above, the meta-analysis conducted by [Berman & Crump \(2008a\)](#) considered the effect of fibre size on lung cancer risk by using data from other studies conducted in similar circumstances as the cohort studies. Their analysis did not reveal strong evidence that lung cancer potency was dependent on fibre size. There was weak evidence that long fibres (length $> 10 \mu\text{m}$) were more potent than short fibres ($5 \mu\text{m} < \text{length} < 10 \mu\text{m}$) in models using all widths ($P = 0.07$). The lack of size-specific data from the studies was a major limitation of this study with regard to estimating size-specific risk estimates. [Stayner et al. \(2008\)](#) published findings from an analysis of the South Carolina asbestos textile cohort in which fibre size specific estimates of lung cancer mortality was evaluated using information from a reanalysis of archived air samples using TEM ([Dement et al., 2008](#)). Long fibres ($> 10 \mu\text{m}$) and thin fibres ($< 0.25 \mu\text{m}$) were found to be the strongest predictors of lung cancer mortality in this study.

Another study not part of the prior meta-analyses provides relevant information regarding the question of the relative lung cancer potency of the fibre types. [Loomis et al. \(2009\)](#) carried out a retrospective cohort mortality study of textile workers from four plants in North Carolina that had never been studied before. Workers in this cohort were primarily exposed to chrysotile asbestos that was imported from Quebec. A small amount of amosite was used in an operation in one of the plants. Overall, an excess of lung cancer was observed in this study (SMR, 1.96; 95%CI: 1.73–2.20), which was very similar in magnitude to that reported in the South Carolina cohort study of textile workers ([Hein et al., 2007](#)).

However, the slope for the exposure–response between asbestos exposure and lung cancer was considerably lower than that reported in the South Carolina cohort study. The reasons for these differences in the exposure–response relationships are unknown, but one possible reason may be that quality of the exposure information was superior in the South Carolina study, and that the difference could be explained by an attenuation of the slope due to exposure misclassification in [Loomis et al. \(2009\)](#).

2.2.2 Environmental exposures

Evidence of an association in women between lung cancer and environmental exposures in New Caledonia to field dust containing tremolite and the use of a whitewash (“po”) containing tremolite has been reported ([Luce et al., 2000](#)). A positive association with heavy residential exposure to asbestos was observed in a lung cancer case–control study the Northern Province of South Africa, which is a crocidolite and amosite mining area ([Mzileni et al., 1999](#)). The association was strongest among women who resided in heavily exposed areas (odds ratio [OR], 5.4; 95%CI: 1.3–22.5; $P_{\text{trend}} = 0.02$). A study of lung cancer mortality among women in two chrysotile mining regions of Quebec did not result in an increase in lung cancer (SMR, 0.99; 95%CI: 0.78–1.25) relative to women from 60 other areas of Canada ([Camus et al., 1998](#)).

2.2.3 Non-commercial asbestiform amphibole fibres

There is emerging epidemiological evidence that non-commercial amphibole fibres that are asbestiform have carcinogenic potential. These fibres are not technically “asbestos,” and they were never commercially marketed. However, the Working Group felt it was important to discuss the recent evidence concerning these

fibres because of their similarity to asbestos, and because of public concerns regarding this issue.

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a), however, they have been more recently described by the US Geological Society as approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported standardized mortality ratios (SMRs), using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs for all cancer (SMR, 1.4; 95%CI: 1.2–1.6; $n = 202$), and lung cancer (SMR, 1.7; 95%CI: 1.4–2.1; $n = 89$). Increasing risks were observed across categories of cumulative exposure; the SMR estimates were 1.5, 1.6, 1.8, and 1.9 in the 1–4.49, 4.5–22.9, 23.0–99.0, and ≥ 100 f/mL-years exposure categories, respectively. Results from other studies (Amandus *et al.*, 1987; McDonald *et al.*, 2004) of analyses using a continuous measure of exposure also resulted in statistically significant relationships with lung cancer mortality risk. For example, in the updated analysis by McDonald *et al.* (2004), the estimated linear increase in relative risk of respiratory cancer risk per 100 f/mL-years cumulative exposure was 0.36 (95%CI: 0.03–1.2; $P = 0.02$).

2.3 Mesothelioma

Pleural and peritoneal mesotheliomas are very rare malignancies that occur in the mesothelial cells that line these cavities. The first report of a possible association between asbestos exposure and mesothelioma was by Wagner *et al.* (1960) who described an outbreak of mesothelioma in a crocidolite mining region of South Africa. The majority of the cases reported had worked in the mines (23/33) but some of the cases had

also occurred among individuals with no history of occupational exposures (10/33). Since then, an excess of mesothelioma has been observed in a large number of cohort and case-control studies (summarized in online Tables 2.2, 2.3 and Table 2.4 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.4.pdf>) in a variety of different industries using and producing asbestos. Although the causal association between mesothelioma and asbestos has been well established, several important issues remain to be resolved that are discussed below.

2.3.1 Fibre type

Although all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos. An excess of mesothelioma has been reported in cohort studies of chrysotile exposed miners and millers in Quebec (Liddell *et al.*, 1997), and in South Carolina asbestos textile workers who were predominantly exposed to chrysotile asbestos imported from Quebec (Hein *et al.*, 2007). However, the fact that the chrysotile asbestos mined in Quebec is contaminated with a small percentage ($< 1.0\%$) of amphibole (tremolite) asbestos has complicated the interpretation of these findings. McDonald *et al.* (1997) found in a nested case-control study for mesothelioma in the Thetford mines of Quebec that an association with asbestos exposure was evident in mines from a region with higher concentrations of tremolite, and not in another region with lower concentrations of tremolite. Bégin *et al.* (1992) noted that although tremolite levels may be 7.5 times higher in Thetford than in Asbestos, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their workforce. This suggests that the tremolitic content of the ores may not be a

determinant of mesothelioma risk in Quebec. Separate analyses for workers at the Thetford and Asbestos mines and mills did not demonstrate a different exposure–response relationship for asbestos and mesothelioma in the two mining areas ([McDonald & McDonald, 1995](#)).

In a mesothelioma case–control study in South Africa, an association was reported with exposures to crocidolite and amosite asbestos, but no cases were found to have been exclusively exposed to chrysotile asbestos ([Rees et al., 1999](#)). One possible explanation for these negative findings for chrysotile is that South African chrysotile asbestos may contain relatively little tremolite ([Rees et al., 1992](#)). Another possible explanation is that chrysotile mining began later, and production levels were lower than in the crocidolite and amosite mines of South Africa. Cases of mesothelioma have been reported among asbestos miners in Zimbabwe, which has been reported to be uncontaminated with tremolite asbestos ([Cullen & Baloyi, 1991](#)). Excess mesothelioma mortality (standardized incidence ratio [SIR], 4.0, 95%CI: 1.5–8.7) was reported in miners and millers from a chrysotile mine in Balangero, Italy ([Mirabelli et al., 2008](#)), reportedly free of amphibole contamination ([Piolatto et al., 1990](#)).

An evaluation of the relative potency of the different fibre types of asbestos has been considered in the meta-analyses that were previously described (see prior section on lung cancer) by [Hodgson & Darnton \(2000\)](#) and [Berman & Crump \(2008a, b\)](#). [Hodgson & Darnton \(2000\)](#) used the percentage of mesothelioma deaths of all deaths expected (at an age of first exposure of 30) per unit of cumulative exposure (Rm) as the measure for their analysis. They computed separate estimates of Rm for crocidolite, amosite and chrysotile asbestos. Based on their analyses, they estimated that the ratio of the potency for mesothelioma (pleural and peritoneal combined) was 1:100:500 for chrysotile, amosite, and crocidolite respectively.

The meta-analysis conducted by [Berman & Crump \(2008a\)](#) was based on the analysis of the slopes (Km) that were estimated using an approach that assumes that the mortality rate from mesothelioma increases linearly with the intensity of exposure, and for a given intensity, increases indefinitely after exposure ceases, approximately as the square of time since first exposure (lagged 10 years). This model was tested with the raw data from several studies, and found to provide a good fit to the data ([Berman & Crump, 2008b](#)). Regression models were fitted to the study Km values that included information from surrogate studies to estimate fibre type (chrysotile versus amphiboles) and fibre length (short versus long) specific potency slopes ([Berman & Crump, 2008a](#)). Alternative models were fitted with exposure metrics based on different fibre widths. The hypothesis that chrysotile and amphibole forms of asbestos are equipotent was strongly rejected, and the hypothesis that potency for chrysotile asbestos was 0 could not be rejected based on their models ($P < 0.001$ and $P = 0.29$, respectively, for all-widths model). The best estimates for the relative potency of chrysotile ranged from zero to about 1/200th that of amphibole asbestos (depending on the width of the exposure metric used in the model). [The Working Group noted that there is a high degree of uncertainty concerning the accuracy of the relative potency estimates derived from the Hodgson & Darnton and Berman & Crump analyses because of the severe potential for exposure misclassification in these studies.]

Two newer studies, not part of the prior meta-analyses, provide important information regarding the question of the relative potency of the fibre types. The first is a study of a cohort of textile workers in North Carolina not previously examined ([Loomis et al., 2009](#)). Workers in this cohort were primarily exposed to chrysotile asbestos imported from Quebec. A relatively large excess of both mesothelioma [SMR, 10.92; 95%CI: 2.98–27.96] and pleural cancer [SMR,

12.43; 95%CI: 3.39–31.83]. The pleural and mesothelioma deaths combined comprised 0.3% of all deaths. This percentage was nearly identical to the estimate developed for the chrysotile cohorts in a review article by [Stayner et al. \(1996\)](#). Based on the approach that Hodgson & Darnton used in their meta-analysis, the authors estimated that the percentage of deaths per unit of fibre exposure was 0.0058% per f-y/mL (0.0098% per f-y/mL for workers followed ≥ 20 years). This estimate was considerably higher than the estimate developed by Hodgson & Darnton of 0.0010% per f-yr/mL for cohorts exposed to chrysotile.

The other study investigated mesothelioma among chrysotile miners and millers, and resident communities in Balangero, Italy. The chrysotile mined at Balangero was reported to be free of tremolite and other amphiboles. The ore contains trace amounts of another fibre called blangeroite, which is not an amphibole ([Turci et al., 2009](#)). A previous cohort of the miners and millers in Balangero with follow up to 1987 identified only two deaths from mesothelioma ([Piolatto et al., 1990](#)). Cases of mesothelioma were identified from a local mesothelioma registry comprises people who had been mine employees; employees of subcontractors or other firms transporting or refining Balangero asbestos, asbestos ore; residents of the area who were exposed from air pollution, living with a mine employee or from mine tailings from Balangero. Six cases of mesothelioma were identified among blue-collar miners, and an estimated 1.5 deaths (SIR, 4.00; 95%CI: 1.47–8.71) would be expected based on a previous cohort study ([Piolatto et al., 1990](#)), and conservative assumptions about the cohort. Additional cases of mesothelioma were identified among white-collar miners (three cases), workers in the mine hired by subcontractors (five cases), and from non-occupational exposures or exposure to re-used tailings (ten cases). Expected numbers of mesothelioma cases could not be derived for these groups because they were not part of the original cohort definition. The

findings from this investigation indicate that the previous risk of mesothelioma for the Balangero cohort were seriously underestimated.

2.3.2 Fibre size

Based on a review of toxicological and human studies, [Lippmann \(1990\)](#) suggested that fibres shorter than 0.1 μm and longer than 5 μm are related to mesothelioma in humans. The Berman & Crump meta-analyses provided weak evidence that fibre length is a determinant of the potency of asbestos. The test of the hypothesis that long fibres (length $\geq 10 \mu\text{m}$) and short fibres ($5 < \text{length} < 10 \mu\text{m}$) are equipotent was nearly rejected in some models (e.g. $P = 0.09$ for all widths). Thus, their findings provide weak support that long fibres may be more potent than short fibres for mesothelioma. There was little evidence in their analyses that thin fibres (width < 0.4 or $< 0.2 \mu\text{m}$) were stronger predictors of mesothelioma potency than all fibre widths combined. A major limitation of their analysis was that it relied on surrogate data to estimate the fibre-size distributions for the studies used in the meta-analysis.

2.3.3 Pleural versus peritoneal tumours

The ratio of pleural to peritoneal mesotheliomas has varied considerably in different epidemiological studies of asbestos-exposed cohorts. In the cohort studies included in the meta-analysis conducted by [Hodgson & Darnton \(2000\)](#), the percentage of mesotheliomas that were peritoneal varied from 0 to over 50%. Hodgson & Darnton reported that peritoneal mesotheliomas increased with the square of cumulative exposure to asbestos (i.e. a supralinear relationship); whereas pleural mesotheliomas increased less than linearly with cumulative exposure to asbestos. This implies that the number of peritoneal mesotheliomas would dramatically increase relative to the number of pleural mesotheliomas at high asbestos exposure levels. [Welch et al.](#)

(2005) found a strong association (OR, 5.0; 95%CI: 1.2–21.5) between asbestos exposure and peritoneal cancer in a population-based case-control study. This study included a large percentage of men with what were judged to be low exposures to asbestos.

2.3.4 Environmental exposures

An excess of mesothelioma has been observed in several studies of communities with environmental exposure to asbestos. A large excess of mesothelioma was reported in a study of people living in villages in Turkey exposed to erionite used to whitewash their homes (Baris *et al.*, 1987). An excess in mesothelioma was reported among people living near crocidolite mining regions in South Africa and Western Australia (Wagner & Pooley, 1986), among people residing in areas of tremolite contamination in Cyprus (McConnochie *et al.*, 1987) and New Caledonia (Luce *et al.*, 2000), and with non-occupational exposures in Europe (Magnani *et al.*, 2000), Italy (Magnani *et al.*, 2001), and California (Pan *et al.*, 2005).

Mesothelioma has also been reported to occur among household members of families of asbestos workers (Anderson *et al.*, 1976; Ferrante *et al.*, 2007).

2.3.5 Non-commercial asbestiform fibres

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a); however, they were subsequently described by the US Geological Society as being composed of approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported SMRs, using cause of death data and expected mortality for the underlying cause of death based on national age-, race-,

and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs, mesothelioma defined by ICD-10 for deaths after 1999 (SMR, 14.1; 95%CI: 1.8–54.4; $n = 2$) and pleural cancer (SMR, 23.3; 95%CI: 6.3–59.5; $n = 4$). The only exposure-response modelling of mesothelioma was presented in the paper by McDonald *et al.*, based on 12 mesothelioma cases (McDonald *et al.*, 2004). Using Poisson regression, the mesothelioma mortality rate across increasing categories of exposure was compared with the rate in the lowest exposure category. For the cumulative exposure metric, the relative risk estimates were 1.0 (referent), 3.72, 3.42, and 3.68, based on 1, 4, 3, and 4, cases, respectively. The mean exposure level in these four quartiles was 8.6, 16.7, 53.2, and 393.8 f/mL-yr, respectively. It should be noted that the referent group was also at excess risk of dying from mesothelioma, i.e. there were 1–3 cases of mesothelioma observed in the referent group, which may have attenuated the observed effects.

A high incidence of mesothelioma was reported among residents of Biancavilla, Italy, a city in eastern Sicily (SMR, 7.21; 95%CI: 3.59–13.00). Reviewing of the work histories of the cases did not indicate an occupational explanation for these exposures, and thus environmental explanations for the mesothelioma excess were sought. Environmental studies have indicated that these mesotheliomas are most likely due to exposures to fluoro-edenite which is a newly recognized fibre that is very similar in morphology and composition to the tremolite-actinolite series (Comba *et al.*, 2003; Bruno *et al.*, 2006; Putzu *et al.*, 2006).

2.4 Other cancer sites

Beyond lung cancer and mesothelioma, the body of literature examining associations between asbestos and other cancers is more sparse. This reflects the fact that lung cancer and mesothelioma have been the principal areas of research

until relatively recently, and other cancers were often not considered in detail in published reports. Clinical and epidemiological studies that span the past five decades suggest, however, that asbestos may be associated with other cancers in addition to lung cancer and mesothelioma. To examine these associations in detail, the US IOM (2006) published a report evaluating the evidence relevant to causation of cancer of the pharynx, larynx, oesophagus, stomach, colon and rectum by asbestos. The present analysis draws on the IOM analysis and presents the most significant positive and negative studies for each anatomical site, with an emphasis on studies that presented data on dose–response as well as on published meta-analyses. Additionally, the present analysis examines the association between asbestos exposure and ovarian cancer, an association that was not examined by the IOM.

2.4.1 Cancer of the pharynx

See Table 2.5 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.5.pdf>.

(a) Cohort Studies

The Working Group examined 16 cohort studies of asbestos and cancer of the pharynx. Some of these studies examined all cancers of the lips, oral cavity, and pharynx. Others restricted their examination to the pharynx itself. Two studies examined only cancers of the hypopharynx. The main findings are summarized in the following paragraphs.

Selikoff & Seidman (1991) observed an SMR for cancer of the oropharynx of 2.18 (95%CI: 1.62–2.91) among a cohort of 17800 male asbestos insulation workers across the USA and Canada. This is the cohort study with the largest number of deaths from pharyngeal cancer, a total of 48 deaths.

Piolatto *et al.* (1990) observed an SMR for cancer of the oropharynx of 2.31 (95%CI:

0.85–5.02; based on six deaths) in a cohort of 1058 asbestos miners in northern Italy exposed to chrysotile asbestos. No association was seen in this cohort between duration of occupational exposure to asbestos and risk of cancer of the pharynx.

Reid *et al.* (2004) observed an SMR for cancer of the pharynx of 1.88 (95%CI: 1.15–3.07; based on 16 deaths) in a cohort of 5685 crocidolite asbestos miners and millers in Western Australia.

Sluis-Cremer *et al.* (1992) observed an SMR for cancer of the lip, oral cavity and pharynx of 2.14 (95%CI: 1.03–3.94; based on 10 deaths) in a cohort of 7317 male asbestos miners in South Africa, some exposed to crocidolite and others to amosite. Cancer of the pharynx was defined in this population as cancer of the lip, oral cavity or pharynx. There was no excess mortality for cancer of the pharynx in the subcohort of amosite asbestos miners (SMR, 0.42; 95%CI: 0.00–1.97), but in the subcohort of crocidolite asbestos miners, the SMR for cancer of the pharynx was 2.94 (95%CI: 1.16–6.18).

Pira *et al.* (2005) observed an SMR for cancer of the pharynx of 2.26 (95%CI: 0.90–4.65; based on seven deaths) in a cohort of 1996 workers in the asbestos textiles industry in Italy.

Other cohort studies of populations occupationally exposed to asbestos in a range of industries contained only small numbers of deaths from cancer of the pharynx (most < 10 deaths), were generally non-positive in their findings, and reported little evidence for dose–response relationships.

(b) Case–control studies

Case–control studies examining the association between asbestos exposure and cancer of the pharynx have two advantages over cohort studies:

1. they are able to collect more cases of this relatively uncommon malignancy; and
2. they are able to adjust for alcohol and tobacco consumption, the two most common causes

of cancer of the pharynx in developed and developing countries.

The present review included six case-control studies. Four of them adjusted for alcohol and tobacco consumption. The main findings are summarized in the following paragraphs.

[Marchand *et al.* \(2000\)](#) carried out a hospital-based, case-control study of 206 cases of cancer of the hypopharynx and 305 controls in France, and found a relative risk of 1.80 (95%CI: 1.08–2.99) in the 161 of their cases ever exposed to asbestos, adjusted for exposure to tobacco and alcohol.

[Berrino *et al.* \(2003\)](#) conducted a multicentre, case-control study of cancer of the hypopharynx in Europe, and found an odds ratio (OR) for “probable” exposure to asbestos of 1.8 (95%CI: 0.6–5.0). This study was restricted to analyses of cancers of the hypopharynx. For cases with “possible” exposure to asbestos, the odds ratio was 1.80 (95%CI: 0.90–3.90). These odds ratios were adjusted for exposure to tobacco and alcohol.

[Zheng *et al.* \(1992\)](#) conducted a population-based, case-control study of cancer of the pharynx in Shanghai, the People’s Republic of China, with 204 incident cancer cases and 414 controls. The relative risk for asbestos exposure was 1.81 (95%CI: 0.91–3.60). Cigarette smoking and alcohol consumption were observed to be positively associated with cancer of the pharynx. By contrast, increasing intake of certain fruits and vegetables, notably oranges, tangerines and Chinese white radishes, appeared to be associated with a reduced risk for cancer of the pharynx.

(c) *Meta-analyses*

The [IOM \(2006\)](#) conducted a meta-analysis of the published cohort studies examining the association between asbestos exposure and cancer of the pharynx. The IOM noted that the findings of the cohort studies were consistently positive. They calculated that the “estimated aggregated relative risk of cancer of the pharynx

from any exposure to asbestos was 1.44 (95%CI: 1.04–2.00). “The IOM noted that few studies had evaluated dose-response trends, and that there was no indication of higher risks associated with more extreme exposures.”

The IOM also conducted a meta-analysis of the case-control studies examining the association between asbestos exposure and cancer of the pharynx. The IOM reported the summary relative risk for cancer of the pharynx in people with “any” exposure to asbestos compared to people with no exposure to be 1.5 (95%CI: 1.1–1.7). The IOM observed that the studies were inconsistent, and that there was little evidence for a dose-response relationship.

2.4.2 *Cancer of the larynx*

See Table 2.5 online.

Cancer of the larynx in relation to asbestos exposure has been studied in a large number of cohort and case-control studies undertaken among occupationally exposed populations in North and South America, Europe, and Asia. ([IOM, 2006](#)).

(a) *Cohort studies*

Cohort studies of workers exposed occupationally to asbestos have found evidence for an association between asbestos exposure and cancer of the larynx across a broad range of industries. The Working Group reviewed 29 cohort studies encompassing 35 populations exposed to asbestos. Noteworthy findings from among these studies are summarized in the following paragraphs.

[Selikoff & Seidman \(1991\)](#) found an SMR for cancer of the larynx of 1.70 (95%CI: 1.01–1.69) among 17800 male insulation workers in the USA and Canada.

[Musk *et al.* \(2008\)](#) found an SMR for cancer of the larynx of 1.56 (95%CI: 0.83–2.67) among 6943 asbestos miners and millers from Western Australia, exposed predominantly to crocidolite

asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last known to be alive, the SMR was 2.57 (95%CI: 1.37–4.39).

[Reid et al. \(2004\)](#) carried out a study of cancer incidence in this same Australian cohort, and found a significant increase in incidence of cancer of the larynx (SIR, 1.82; 95%CI: 1.16–2.85).

[Piolatto et al. \(1990\)](#) found an SMR for cancer of the larynx of 2.67 (95%CI: 1.15–5.25; based on eight deaths) in a cohort study of 1058 male asbestos miners in northern Italy. In the subset of this cohort with > 20 years' exposure to asbestos, the SMR for cancer of the larynx was 4.55 (95%CI: 1.47–10.61). There was evidence of a positive dose–response relationship between cumulative exposure to asbestos dust, measured as fibre–years, and risk of death from cancer of the larynx. The SMRs for cancer of the larynx were 1.43 (95%CI: 0.04–7.96) in workers with exposure < 100 fibre–years; 2.22 (95%CI: 0.27–8.02) in workers with exposure of 100–400 fibre–years; and 3.85 (95%CI: 1.25–8.98) in workers with cumulative exposure > 400 fibre–years.

[Peto et al. \(1985\)](#) found an overall SMR for cancer of the larynx of 1.55 (95%CI: 0.42–3.97; based on four deaths) in a cohort of 3211 asbestos-textile workers in the United Kingdom. When workers were subdivided according to time since first employment, and by duration of employment in “scheduled” (asbestos-exposed) areas of the plant, four deaths from cancer of the larynx were observed in the most heavily exposed group versus 1.53 expected (SMR, 2.55).

[Pira et al. \(2005\)](#) found an overall SMR for cancer of the larynx of 2.38 (95%CI: 0.95–4.90; based on seven deaths—all of them in male workers) in a cohort of 889 men and 1077 women employed in an asbestos textiles plant in Italy.

[Raffin et al. \(1989\)](#) found an overall SIR for cancer of the larynx of 1.66 (95%CI: 0.91–2.78) in a cohort study of 7986 men and 584 women employed in the asbestos-cement industry in

Denmark. However, in the subset with > 5 years employment, the SIR was 2.27 (95%CI: 0.83–4.95), and in the group first employed from 1928–40, the SIR was 5.50 (95%CI: 1.77–12.82).

(b) Case–control studies

Case–control studies are important in examining relationships between asbestos exposure and cancer of the larynx, because they overcome the relative rarity of the diagnosis in cohort studies, and also because they permit consideration of potential confounding by exposure to tobacco and alcohol, the two most important risk-factors for this malignancy in developed and developing countries.

The Working Group analysed 15 case–control studies of asbestos and cancer of the larynx. This analysis revealed that 14 of the 15 published studies had found evidence for a significantly positive association between asbestos exposure and cancer of the larynx; only one study ([Luce et al., 2000](#)) reported an odds ratio below 1.0.

(c) Meta-analyses

The IOM conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the larynx. For studies examining “any” versus no exposure, the summary relative risk was 1.4 (95%CI: 1.19–1.64). For studies comparing “high” exposure versus no exposure, the lower bound summary relative risk was 2.02 (95%CI: 1.64–2.47), and the upper bound summary relative risk was 2.57 (95%CI: 1.47–4.49).

The IOM also conducted a meta-analysis of the published case–control studies examining the association between asbestos exposure and cancer of the larynx ([IOM, 2006](#)). This meta-analysis calculated a summary relative risk of 1.43 (95%CI: 1.15–1.78), before adjusting for consumption of tobacco and alcohol. After adjusting for tobacco and alcohol consumption, the association of cancer of the larynx with

asbestos exposure persisted, with an adjusted summary relative risk of 1.18 (95%CI: 1.01–1.37).

2.4.3 Cancer of the oesophagus

See Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.6.pdf>.

(a) Cohort studies

The Working Group examined 25 studies of cohorts occupationally exposed to asbestos. Notable findings from among these studies are:

[Selikoff & Seidman \(1991\)](#) found an SMR for cancer of the oesophagus of 1.61 (95%CI: 1.13–2.40) among a cohort of 17800 asbestos insulations workers across the USA and Canada. [Selikoff & Seidman \(1991\)](#) observed that cancer in asbestos workers is “very much related to latency,” with most of the increased risk occurring only 25 or more years from the onset of occupational exposure to asbestos.

In a cohort of 10939 male and 440 female asbestos miners and millers in Quebec, Canada, exposed predominantly to chrysotile asbestos, followed through 1975, [McDonald et al. \(1980\)](#) reported that mortality for cancer of the oesophagus and stomach (the two were combined) was elevated (SMR, 1.27). Further follow-up through 1988 of a subset of this cohort, consisting of 5335 men, examined esophageal cancer mortality separate from stomach cancer and found no excess mortality (SMR, 0.73; 95%CI: 0.35 – 1.34) ([McDonald et al., 1993](#)).

[Musk et al. \(2008\)](#) found an SMR for cancer of the oesophagus was 1.01 (95%CI: 0.71–1.40) in a cohort study of 6943 asbestos miners from Western Australia followed through 2000, exposed predominantly to crocidolite asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last known to be alive, the SMR was 1.20 (95%CI: 0.62–2.10).

[Hein et al. \(2007\)](#) found an SMR for cancer of the oesophagus of 1.87 (95%CI: 1.09–2.99) in a cohort of 3072 asbestos textile workers in South Carolina, occupationally exposed to chrysotile asbestos and followed through 2001.

[Peto et al. \(1985\)](#) found 11 deaths from cancer of the oesophagus versus 6.59 expected (SMR = 1.67; 95%CI: 0.83–2.99) in a cohort of 3211 male asbestos textile workers in the United Kingdom. For the subset of workers with 10+ years employment in “scheduled” (asbestos-exposed) areas of the plant and with 20+ years since first employment, the SMR for cancer of the oesophagus was 2.36 (95%CI: 0.49–6.91). For all workers in this cohort with < 20 years since first employment, two deaths for cancer of the oesophagus was observed versus 2.18 expected, and for workers with 20+ years since first employment, there were nine deaths from cancer of the oesophagus versus 4.4 expected (see Table 6 in [Peto et al., 1985](#)).

[Berry et al. \(2000\)](#) found a 2-fold excess mortality for cancer of the oesophagus (SMR, 2.08; 95%CI: 1.07–3.63) among a cohort of over 5000 asbestos-exposed factory workers in the east end of London, United Kingdom, who had produced asbestos insulation boards, and who were followed for 30+ years. In the subset of workers within this population with “severe” asbestos exposure of more than 2 years’ duration, the SMR for cancer of the oesophagus was 5.62 (95%CI: 1.82 – 13.11). And in the subset of women with “severe” exposure to asbestos of > 2 years, the SMR for cancer of the oesophagus was 9.09 (95%CI: 1.10–32.82).

Other cohort studies of various groups occupationally exposed to asbestos – asbestos-cement workers, friction products workers, and “generic” asbestos workers – yield generally non-positive results for cancer of the oesophagus.

(b) Case-control studies

The Working Group examined five case-control studies that examined the association between asbestos exposure and cancer of the oesophagus.

A case-control study in Quebec, Canada found an OR of 2.0 (95%CI: 1.1–3.8) for any exposure to asbestos among 17 patients diagnosed with squamous cell carcinoma of the oesophagus. ([Parent et al., 2000](#)).

A case-control study conducted within a cohort of nearly 400000 Swedish construction workers found evidence for a positive association between asbestos exposure and adenocarcinoma of the oesophagus. Relative risk increased from 1.0 (reference) among workers with no asbestos exposure, to 1.7 (95%CI: 0.5–5.4) among those with “moderate” exposure, and to 4.5 (95%CI: 1.4–14.3) among those workers with “high” asbestos exposure, thus suggesting a positive dose-response relationship ([Jansson et al., 2005](#)).

(c) Meta-analyses

Meta-analyses have been undertaken of the association between asbestos exposure and cancer of the oesophagus:

A meta-analysis by [Frumkin & Berlin \(1988\)](#) stratified studies according to SMR for lung cancer and also according to the percentage of deaths due to mesothelioma. The rationale is that a higher death rate for either lung cancer or mesothelioma is taken to be a surrogate index of higher cumulative exposure to asbestos. However, no association was observed between death rate for cancer of the oesophagus in the published cohorts by either lung cancer SMR or percentage of death for mesothelioma.

Meta-analyses by [Edelman \(1988\)](#) and by [Goodman et al. \(1999\)](#) did not detect an association between asbestos exposure and cancer of the oesophagus.

A meta-analysis by [Morgan et al. \(1985\)](#) that examined earlier studies, which tended to have

heavier exposure, found a summary SMR for cancer of the oesophagus in asbestos-exposed workers of 2.14 (95%CI: 1.326–3.276). When cases of cancer of the oesophagus based on “best evidence” (pathological review) were deleted from these cohorts, the SMR remained elevated at 2.38 (95%CI: 1.45–3.68).

The [IOM \(2006\)](#) conducted a meta analysis of 25 cohort studies and reported a summary relative risk of 0.99 (95%CI: 0.78–1.27) for any exposure to asbestos versus no exposure. The IOM also examined the relative risk of “high” versus no exposure, and calculated a lower bound summary relative risk of 1.35 (95%CI: 0.81–2.27), and a higher bound summary relative risk of 1.43 (95%CI: 0.79–2.58). The IOM determined that there were too few case-control studies to permit a meta-analysis.

2.4.4 Cancer of the stomach

The Working Group reviewed 42 cohort studies and five population-based case-control studies that examined the association between asbestos and cancer of the stomach (See Table 2.6 online).

(a) Cohort studies

Notable findings among the cohort studies are:

[Selikoff et al. \(1964\)](#) reported a nearly 3-fold excess mortality for cancer of the stomach (12 observed versus 4.3 expected) in a population of 632 insulation workers in New York and New Jersey occupationally exposed to asbestos dust. Further analysis within this cohort ([Selikoff et al., 1979](#)) found evidence of a dose-response relationship between duration of exposure to asbestos (in years), and risk of death from cancer of the stomach. The SMR for cancer of the stomach increased from 0.00 in workers exposed for < 20 years, to 4.00 (95%CI: 1.47 – 8.71) in those exposed for 20 – 35 years, and to 3.42 (95%CI: 1.82 – 5.85) in those exposed for > 35 years.

[Selikoff et al. \(1967\)](#) found a modest, non-significant increase in risk of death for cancer of the stomach: 34 observed v. 29.4 expected, (SMR = 1.16; 95%CI: 0.92 – 1.78) in a larger cohort study of 17800 insulation workers across the USA and Canada. No data on dose-response for cancer of the stomach were presented in this analysis.

[Liddell et al. \(1997\)](#) reported an overall SMR for cancer of the stomach of 1.24 (95%CI: 1.07 – 1.48) in a study of 10918 asbestos miners and millers exposed predominantly to chrysotile asbestos, in Quebec, Canada. Within this cohort, a positive dose-response relationship was observed between cumulative exposure to asbestos dust (mcpf-year) and mortality for cancer of the stomach. Thus, for workers with cumulative dust exposure < 300, the SMR was 1.16; for workers with cumulative exposure of 300 – 400, the SMR was 1.29; for workers with cumulative exposure of 400 – 1000, the SMR was 1.21; and for workers in the highest exposure category, with cumulative exposure > 1000, the SMR was 3.21 (95%CI: 1.87 – 5.14). An additional finding in this cohort was a modest interaction between cumulative asbestos exposure, cigarette smoking, and mortality from cancer of the stomach.

[Musk et al. \(2008\)](#) found an SMR for cancer of the stomach of 1.01 (95%CI: 0.71 – 1.40) in a cohort of 6943 asbestos miners and millers exposed predominantly to crocidolite asbestos in Wittenoom, Western Australia, followed through the end of 2000, and when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring subjects at the date last known to be alive, the SMR was 1.71 (95%CI: 1.20 – 2.35).

[Reid et al. \(2004\)](#) conducted a nested case-control study within this same Australian cohort, and found a positive exposure-response relationship between cancer of the stomach and cumulative exposure to asbestos (test for trend, $P = 0.057$). No association was seen between

cancer of the stomach and either time since first exposure or year of starting work with asbestos. Smoking status was associated with cancer of the stomach, but not significantly.

[Meurman et al. \(1974\)](#) found a non-significant increase in SMR for cancer of the stomach: SMR = 1.42 (95%CI: 0.76 – 2.43) in a cohort of 736 asbestos miners in Finland exposed to anthophyllite asbestos.

[Berry et al. \(2000\)](#) found a modest, non-significant increased risk for death from cancer of the stomach: 28 observed versus 23.1 expected (SMR, 1.21; 95%CI: 0.81–1.75) in a British study of factory workers producing asbestos insulation in the east end of London.

Strongly positive dose-response associations between cumulative asbestos response and cancer of the stomach were observed in two cohort studies of Chinese factory workers – one in Beijing and the other in Qingdao; relative risks for cancer of the stomach were 4.4 and 2.4, respectively ([Zhu & Wang, 1993](#); [Pang et al., 1997](#)).

[Raffn et al. \(1989\)](#) observed 43 deaths from cancer of the stomach versus 30.09 expected (SMR, 1.43; 95%CI: 1.03 – 1.93) in a cohort of 7986 men employed from 1928–84 in the asbestos cement industry in Denmark.

[Enterline et al. \(1987\)](#) observed a SMR for cancer of the stomach of 1.80 (95%CI: 1.10–2.78) in a cohort of 1074 retired US asbestos workers.

Epidemiological studies of cohorts with asbestos-related diseases – asbestosis and benign pleural disease – have not found increased mortality for cancer of the stomach ([Germani et al., 1999](#); [Karjalainen et al., 1999](#); [Szeszenia-Dabrowska et al., 2002](#)).

(b) Case-control studies

Case-control studies exploring the relationship between asbestos exposure and cancer of the stomach yield inconsistent results. The Working Group reviewed five case-control studies. Notable findings are these:

A study from Poland ([Krstev et al., 2005](#)) found an OR for cancer of the stomach of 1.5 (95%CI: 0.9–2.4) for workers ever exposed to asbestos, and of 1.2 (95%CI: 0.6–2.3) for workers with 10 or more years of exposure to asbestos.

The largest case–control study to examine the association between asbestos and cancer of the stomach ([Cocco et al., 1994](#)) reported an odds ratio of 0.7 (95%CI: 0.5–1.1) for workers ever exposed to asbestos, and of 1.4 (95%CI: 0.6–3.0) for those with 21+ years of exposure to asbestos.

The most strongly positive case–control study linking asbestos to cancer of the stomach is the case–control study, cited above, nested within the Western Australia mining cohort ([Reid et al., 2004](#)).

(c) *Meta-analyses*

Several meta-analyses have been undertaken of the association between asbestos exposure and cancer of the stomach.

A meta-analysis by [Frumkin & Berlin \(1988\)](#) stratified studies according to SMR for lung cancer and also according to percentage of deaths due to mesothelioma. Frumkin & Berlin found in cohorts where the SMR for lung cancer was < 2.00 that the SMR for cancer of the stomach was 0.91 (95%CI: 0.71–1.16). By contrast, when the SMR for lung cancer was > 2.00, the SMR for cancer of the stomach increased to 1.34 (95%CI: 1.07–1.67).

[Gamble \(2008\)](#) reported that point estimates for cancer of the stomach mortality tended towards 1.0 when the excess risk for lung cancer were less than 4-fold, but “tended to be somewhat elevated when lung cancer relative risks were 4-fold or greater.” Gamble observed further that “combined relative risks for cancer of the stomach stratified by lung cancer categories showed a suggestive trend, with a significant deficit (0.80) when lung cancer SMRs were <1.0 that increased monotonically to a significant 1.43-fold excess in the studies with lung cancer SMRs > 3.0.” Gamble observed no trend for increasing SMR for cancer

of the stomach with increasing percentage of deaths from mesothelioma ([Gamble, 2008](#)).

The [IOM \(2006\)](#) conducted a meta-analysis of 42 cohort studies examining the association between asbestos exposure and cancer of the stomach. The IOM noted that the “majority of cohort relative risk estimates for cancer of the stomach exceed the null value (1.0), indicating excesses, although estimates varied considerably in strength.” In cohorts that compared “any” versus no exposure, the summary relative risk was 1.17 (95%CI: 1.07–1.28). The IOM notes that with respect to dose–response, the summary estimates were stable. Thus in the cohorts that compared “high” versus no exposure, the lower bound summary relative risk was 1.31 (95%CI: 0.97–1.76), and the higher bound summary relative risk, 1.33 (95%CI: 0.98–1.79).

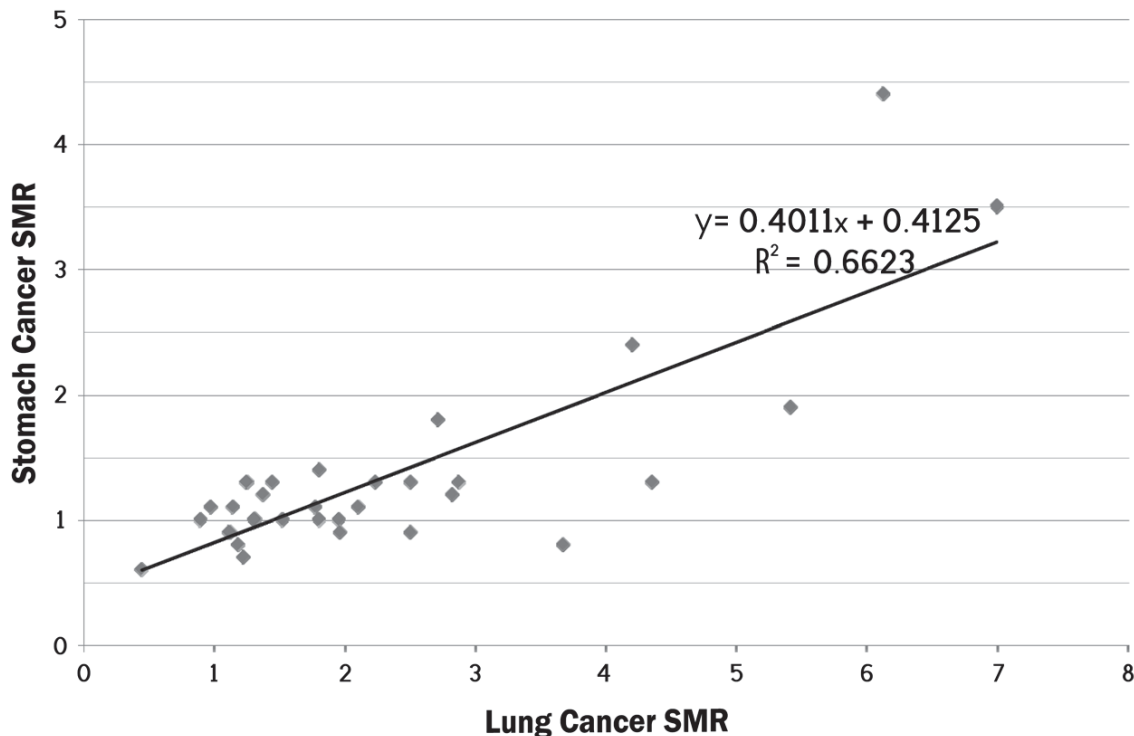
The IOM conducted a meta-analysis of the five case–control studies resulting in a combined relative risk of 1.11 (95%CI: 0.76–1.64). The summary odds ratio increased when only extreme exposure was considered (OR, 1.42; 95%CI: 0.92–2.20).

The Working Group developed a scatter plot comparing SMRs for lung cancer with SMRs for cancer of the stomach in the same cohorts. A positive trend was observed between the two, and the correlation coefficient (r^2) = 0.66, see Fig. 2.1.

(i) *Asbestos in drinking-water and cancer of the stomach*

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the stomach. These studies correlated population exposure to asbestos in water supplies with population cancer rates. [Levy et al. \(1976\)](#) reported an excess in cancer of the stomach among persons in Duluth, MN, USA exposed to taconite asbestos in drinking-water. [Wigle \(1977\)](#) saw an excess of male cancer of the stomach among some exposed to asbestos in drinking-water in Quebec. [Conforti et al. \(1981\)](#)

Fig 2.1 Stomach & lung cancer correlation in asbestos cohorts



Compiled by the Working Group

saw a similar association in the San Francisco Bay area, USA. [Polissar *et al.* \(1982\)](#) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. They observed no association between asbestos exposure and cancer of the stomach. A similarly negative study was observed in a study conducted in Woodstock, NY, USA ([Howe *et al.*, 1989](#)).

[Kjærheim *et al.* \(2005\)](#) examined cancer of the stomach incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. They found an SIR for cancer of the stomach in the entire cohort of 1.6 (95%CI: 1.0–2.3). In the subcohort with “definite” exposure to asbestos, the SIR was 2.5 (95%CI: 0.9–5.5). In those members of the definite exposure subcohort

followed for 20+ years, the SIR was 1.7 (95%CI: 1.1–2.7).

[Cantor \(1997\)](#) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and cancer of the stomach, and concluded that the available data were inadequate to evaluate the cancer risk of asbestos in drinking-water.

[Marsh \(1983\)](#) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada, and found no consistent pattern of association.

2.4.5 Cancer of the colorectum

The Working Group examined data from 41 occupational cohorts and 13 case-control studies that reported data on associations between asbestos exposure and cancer of the colon and rectum (See Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.7.pdf>). The Working Group made the decision to combine information on these two sites, although a few comments in several places in the text about the two sites considered separately have also been made.

(a) Cohort studies

An association between occupational exposure to asbestos and cancer of the colorectum was first reported in 1964 by Selikoff *et al.* in a cohort of 632 male insulation workers in New York and New Jersey, USA (Selikoff *et al.*, 1964). Further analysis of this cohort found a positive relationship between duration of work with asbestos and risk of cancer of the colorectum, in that the SMR increased from 0.00 (95%CI: 0.00–18.45) in workers with < 20 years exposure, to 3.68 (95%CI: 1.48–7.59) among workers with 20–35 years' exposure, and to 2.58 (95%CI: 1.48–4.19) among workers with the longest duration of exposure, > 35 years (Selikoff & Hammond, 1979).

Selikoff *et al.* (1967), in a second report, found an association between occupational exposure to asbestos and cancer of the colorectum in a population of 17800 asbestos insulators across the USA and Canada (SMR, 1.37; 95%CI: 1.14–1.64).

Seidman *et al.* (1986) reported an elevated mortality from cancer of the colorectum in a population of 820 male factory workers in Paterson, NJ, USA, exposed to amosite asbestos (SMR, 2.77; 95%CI: 1.16–2.80). They noted that cancer of the colorectum in asbestos workers tended to be a disease of long latency; they reported that the ratio of observed to expected

deaths increased with increasing interval since initial exposure to asbestos.

McDonald *et al.* (1980) reported an overall SMR for cancer of the colorectum of only 0.78 in a study of 10939 men and 440 women workers employed as asbestos miners and millers in Quebec with predominant exposure to chrysotile asbestos. Additionally, however, McDonald *et al.* reported a “clear trend for SMRs to be higher, the heavier the exposure.” Thus with increasing levels of cumulative occupational exposure to asbestos dust, relative risks for cancer of the colorectum increased in this cohort from 1.00 in workers with less than 30 mpcf-y cumulative exposure, to 0.93 in workers with 30–300 mpcf-y, to 1.96 in workers with 300–1000 mpcf-y, and then in the group with heaviest exposure, > 1000 mpcf-y, to 5.26.

Albin *et al.* (1990) found an overall SMR for cancer of the colorectum of only 1.5 (95%CI: 0.7–3.0) in a cohort of 1465 asbestos-cement workers in Sweden. A positive association between asbestos exposure and cancer of the colorectum was reported, but when cancer of the colorectum mortality was examined by individual cumulative exposure to asbestos, measured as fibre-years/mL, the SMR was 1.3 (95%CI: 0.5–2.9) for those workers with cumulative exposure of < 15 fibre-years/mL; for those with cumulative exposure of 15–39 fibre-years/mL, the SMR was 1.1(95%CI: 0.3–3.9); and for those workers in highest exposure category with > 40 fibre-years/mL, the SMR for cancer of the colorectum was 3.4 (95%CI: 1.2–9.5). Diagnosis in all but one of the cancers in the highest exposure category was verified by pathological review, and no case of certified or probable mesothelioma was found. The trend towards increasing mortality from cancer of the colorectum with increasing cumulative exposure to asbestos was statistically significant ($P = 0.04$). A similar trend was seen for cancer of the colorectum morbidity.

Excess mortality from colon cancer was observed in a heavily exposed cohort of over

5000 workers in the east end of London, who had produced asbestos insulation board and were followed for 30+ years ([Berry et al., 2000](#)). The overall SMR for colon cancer in this cohort was 1.83 (95%CI: 1.20–2.66). There was evidence for a positive dose–response relationship, in that excess mortality from colon cancer was confined to men who had worked as ladders or had been severely exposed for more than 2 years. This positive trend was statistically significant ($P = 0.017$).

In a cohort comprised of family members of men who had been employed in an asbestos-cement factory in Casale Monferrato, Italy, [Ferrante et al. \(2007\)](#) examined cancer mortality. Among women with domestic exposure to asbestos, 21 deaths from cancer of the “intestine and rectum” versus 16.0 expected (SMR, 1.31; 95%CI: 0.81–2.0) were observed. For cancer of the rectum, ten deaths versus five expected (SMR, 2.00; 95%CI: 0.96–3.69) were observed.

Several other cohort studies of occupationally exposed populations in a variety of industries have also found evidence for an association between asbestos exposure and cancer of the colorectum ([Puntoni et al., 1979](#); [Hilt et al., 1985](#); [Jakobsson et al., 1994](#); [Raffin et al., 1996](#); [Szeszenia-Dabrowska et al., 1998](#); [Smaylyte et al., 2004](#)).

[Jakobsson et al. \(1994\)](#) examined colon cancer by anatomical location in asbestos-cement workers, and observed an increased incidence of malignancy in the right side of the colon, but not in the left side.

A report on incidence of cancer of the colorectum from the Beta-Carotene and Retinol Efficacy Trial (CARET) found a relative risk of 1.36 (95%CI: 0.96–1.93) among 3987 heavy smoker participants occupationally exposed to asbestos as compared to smoker participants not exposed to asbestos ([Aliyu et al., 2005](#)). Of note was the finding that the relative risk for cancer of the colorectum was 1.54 (95%CI: 0.99–2.40) among participants with asbestos-induced pleural plaques. The investigators interpreted the

presence of pleural plaques as a marker for heavy individual exposure to asbestos. Risk for cancer of the colorectum also increased with worsening pulmonary asbestosis ($P = 0.03$ for trend). It was reported that a “dose–response trend based on years of asbestos exposure was less evident”.

(b) Case–control studies

Evidence from case–control studies of asbestos and cancer of the colorectum is in general less strong than the evidence from the cohort studies. However, case–control studies from the Nordic countries and the USA have, however, reported significant increases in asbestos-associated odds ratios in occupationally exposed populations ([Fredriksson et al., 1989](#); [Gerhardsson de Verdier et al., 1992](#); [Vineis et al., 1993](#); [Kang et al., 1997](#); [Goldberg et al., 2001](#)).

Consideration of latency since first exposure appears to be an important factor in assessing these studies. Thus, [Gerhardsson de Verdier et al. \(1992\)](#) examined incidence of cancer of the colorectum by interval since first occupational exposure and observed “for subjects exposed to asbestos, the risks were highest when the latency period was more than 39 years.” [Gerhardsson de Verdier et al.](#) observed further that the relative risk for cancer of the right colon was 2.6 (95%CI: 1.2–5.9) among workers exposed to asbestos, and that for malignancy of the left colon, only 0.5 (95%CI: 0.1–1.9).

Other cohort and case–control studies have not found evidence for an association between asbestos exposure and cancer of the colorectum ([Gardner et al., 1986](#); [Hodgson & Jones, 1986](#); [Garabrant et al., 1992](#); [Dement et al., 1994](#); [Demers et al., 1994](#); [Tulchinsky et al., 1999](#); [Hein et al., 2007](#); [Loomis et al., 2009](#)).

(c) Meta-analyses

Some of these meta-analyses have stratified studies according to the standardized mortality ratio for lung cancer or the percentage of deaths due to mesothelioma:

[Morgan et al. \(1985\)](#) found a summary standardized mortality ratio for cancer of the colorectum of 1.13 (95%CI: 0.97–1.30). This was reduced to 1.03 (95%CI: 0.88–1.21) after deleting cases in which the diagnosis of cancer of the colorectum was based on “best evidence” (pathological review) rather than death certificate data.

[Frumkin & Berlin \(1988\)](#) found in cohorts where the standardized mortality ratio for lung cancer was < 2.00 that the standardized mortality ratio for cancer of the colorectum was 0.86 (95%CI: 0.69–1.09). By contrast, when the standardized mortality ratio for lung cancer was > 2.00, the standardized mortality ratio for cancer of the colorectum increased to 1.61 (95%CI: 1.34–1.93).

[Homa et al. \(1994\)](#) found an elevated summary standardized mortality ratio for cancer of the colorectum in cohorts exposed to serpentine asbestos that had an standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.73; 95%CI: 0.83–3.63), and also in cohorts exposed to a mix of amphibole and serpentine asbestos that had a standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.48; 95%CI: 1.24–1.78). Among cohorts exposed to amphibole asbestos, the standardized mortality ratio for cancer of the colorectum was elevated regardless of the standardized mortality ratio for lung cancer. [Homa et al. \(1994\)](#) saw similar trends between standardized mortality ratio for cancer of the colorectum and percentage of deaths from mesothelioma.

[Gamble \(2008\)](#) reported that there was “tendency for CRC [cancer of the colorectum] risk ratios to be elevated when lung cancer risk ratios are >4” and further noted a significantly elevated standardized mortality ratio of 1.60 (95%CI: 1.29–2.00) for cancer of the colorectum when the standardized mortality ratio for lung cancer exceeds 3.00. [Gamble \(2008\)](#) observed no trend in cancer of the colorectum mortality with

increasing percentage of deaths due to mesothelioma. Gamble saw no association between asbestos exposure and rectal cancer.

The [IOM \(2006\)](#) conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the colorectum. In studies that compared “any” versus no exposure, the summary relative risk was 1.15 (95%CI: 1.01–1.31). For studies comparing “high” versus no exposure, the lower-bound summary relative risk was 1.24 (95%CI: 0.91–1.69), and the upper-bound summary relative risk, 1.38 (95%CI: 1.14–1.67).

The IOM also conducted a meta-analysis of the published case-control studies. Overall, 13 studies comparing “any” versus no exposure yielded a summary relative risk of 1.16 (95%CI: 0.90–1.49).

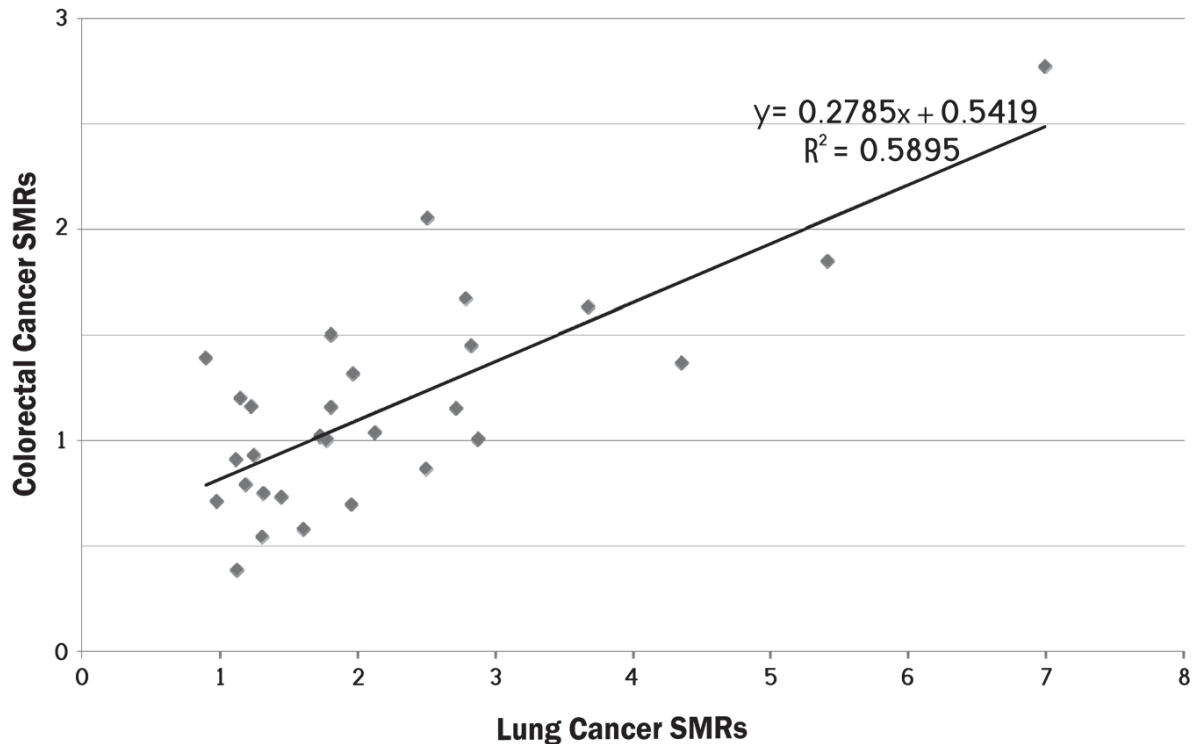
The *IARC Monograph 100C* Working Group developed a scatter plot comparing standardized mortality ratios for lung cancer with standardized mortality ratios for cancer of the colorectum in the same cohorts. The trend was positive with a correlation coefficient (r^2) of 0.59, see Fig. 2.2.

(i) *Asbestos in drinking-water and cancer of the colorectum*

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the colon. These studies correlated population exposure to asbestos in water supplies with population cancer rates. [Polissar et al. \(1982\)](#) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. No association between asbestos exposure and colon cancer was observed. A similarly negative study was observed in a study conducted in Woodstock, NY, USA ([Howe et al., 1989](#)).

[Kjærheim et al. \(2005\)](#) examined colon cancer incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. The standardized incidence ratio for colon cancer in

Fig 2.2 Colorectal & lung cancer correlation in asbestos cohorts



Compiled by the Working Group

the entire cohort was 1.5 (95%CI: 0.9–2.2). In the subcohort with “definite” exposure to asbestos, the standardized incidence ratio was 0.8 (95%CI: 0.1–2.9). In those members of the definite exposure subcohort followed for 20+ years, the standardized incidence ratio was 1.6 (95%CI: 1.0–2.5).

[Cantor \(1997\)](#) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and colon cancer and concluded that the data were inadequate to evaluate colon cancer risk of asbestos in drinking-water.

[Marsh \(1983\)](#) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and

Canada and found no consistent pattern of association.

2.4.6 Cancer of the ovary

The published literature examining the association between asbestos exposure and cancer of the ovaries is relatively sparse, because the workforce occupationally exposed to asbestos in such occupations as mining, milling shipyard work, construction and asbestos insulation work has been predominantly male. An examination of the association between asbestos and ovarian cancer was not undertaken by the [IOM \(2006\)](#).

See Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.8.pdf>.

(a) *Cohort studies*

The Working Group examined 11 cohort studies that examined the association between asbestos exposure and ovarian cancer in 13 populations, ten with occupational exposure to asbestos and three with community-based or residential exposure.

[Acheson et al. \(1982\)](#) examined a cohort in the United Kingdom consisting of two groups of women in separate factories ($n = 1327$), employed in the manufacture of asbestos-containing gas masks before and during World War II. One factory had used crocidolite asbestos, and the other had used chrysotile. Among 757 women in the plant that used crocidolite, 12 deaths from ovarian cancer were observed versus 4.4 expected (SMR, 2.75; 95%CI: 1.42–4.81). Among 570 women in the plant that used chrysotile asbestos, five deaths were observed for ovarian cancer versus 3.4 expected (SMR, 1.48; 95%CI: 0.48–3.44).

[Wignall & Fox \(1982\)](#) conducted a 30-year, follow-up mortality study of a population of 500 women in the United Kingdom employed in the manufacture of asbestos-containing gas masks before and during World War II. The type of asbestos used was crocidolite. A total of six deaths from ovarian cancer were observed versus 2.8 expected (SMR, 2.13). When the cohort was subdivided according to degree of exposure to asbestos, the highest mortality from ovarian cancer was found among the subgroup definitely exposed to asbestos from the early 1940s (SMR, 14.81; $P < 0.01$). Overall five deaths from ovarian cancer were found among women definitely exposed to asbestos (versus 0.63 expected), whereas none were found among women definitely not exposed to asbestos (versus 0.40 expected).

To address potential misclassification of some deaths in this cohort recorded on death certificates as ovarian cancer as opposed to peritoneal mesothelioma, [Wignall & Fox \(1982\)](#) conducted a histopathological review of the cases of diagnosed ovarian cancer for which tissue material was available. One of these three cases was found to be peritoneal mesothelioma, while the diagnosis of ovarian cancer was sustained in the other two cases.

In a cohort study of 700 women factory workers employed in an asbestos-board insulation manufacturing company in the east end of London and followed for 30+ years, [Berry et al. \(2000\)](#) observed nine deaths from ovarian cancer versus 3.56 expected (SMR, 2.53; 95%CI: 1.16–4.80) ([Berry et al., 2000](#)), with evidence for a positive exposure–response relationship. Among women with low-to-moderate exposure to asbestos, two deaths were observed versus 0.54 expected; in the subset with “severe” asbestos exposure of < 2 years’ duration, two deaths were observed versus 2.12 expected. (SMR, 0.94); and among women with severe exposure of > 2 years’ duration, five deaths from ovarian cancer were observed versus 0.90 expected (SMR, 5.35).

An assessment was performed of the significance of the positive exposure–response trend ($P = 0.18$). To address the potential misclassification of some deaths in this cohort having been recorded as ovarian cancer as opposed to peritoneal mesothelioma, [Newhouse et al. \(1972\)](#) conducted a histopathological review of the four deaths that by 1972 had been recorded as due to ovarian cancer; three of the four had occurred in women with severe and prolonged exposure to asbestos. Histological material was available for two of these cases. In both, the diagnosis of ovarian cancer was confirmed.

[Reid et al. \(2008\)](#) reported on cancer mortality in a cohort of 2552 women and girls who lived in the crocidolite asbestos mining town of Wittenoom in Western Australia during 1943–92, who were not involved in asbestos

mining and milling. Environmental contamination of the town with asbestos dust is reported to have been extensive. The women's exposure was environmental and not occupational. There were nine deaths from ovarian cancer in this cohort (SMR, 1.26; 95%CI: 0.58–2.40).

[Reid et al. \(2009\)](#) conducted a cancer incidence study in the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos. Additionally, they examined cancer incidence in 416 women who had worked in various capacities in the Wittenoom crocidolite asbestos mines and mills. Among community residents, ten incident cases of ovarian cancer were observed (SIR, 1.18; 95%CI: 0.45–1.91). Among women workers employed in the asbestos factory, one case of ovarian cancer was observed (SIR, 0.49; 95%CI: 0.01–2.74).

To address the possibility that some diagnosed cases of ovarian cancer in this cohort might in fact have been cases of peritoneal mesothelioma, [Reid et al. \(2009\)](#) examined pathological material from nine of their cases. The diagnosis of ovarian cancer was sustained in every case.

[Pira et al. \(2005\)](#) conducted a cohort study of 1077 women employed for at least one month during 1946–84 in an asbestos-textile factory in Italy, and followed up to 1996. A variety of types of asbestos were used in the factory, including crocidolite. A non-significantly increased standardized mortality ratio of 2.61 was observed for cancer of the ovary, based on five deaths. Among women in this cohort with ≥ 10 years of employment with asbestos, the standardized mortality ratio for ovarian cancer was 5.73, based on three deaths. Among women with ≥ 35 years since first employment, the standardized mortality ratio for ovarian cancer was 5.37, based on two deaths. This cohort was heavily exposed to asbestos, as supported by a standardized mortality ratio for lung cancer among women of 5.95, and by the occurrence of 19 deaths from mesothelioma (12%) among 168 total deaths in women.

[Magnani et al. \(2008\)](#) examined cancer mortality among a cohort of former workers at a now closed asbestos-cement factory in Casale Monferrato, Italy. A mix of crocidolite and chrysotile asbestos was used in this factory. Among women workers, there was an excess of ovarian cancers: nine observed versus 4.0 expected (SMR, 2.27; $P < 0.05$). Among women workers with 30 or more years exposure, the standardized mortality ratio for ovarian cancer was 2.97. [Bertolotti et al. \(2008\)](#) described the same findings in the same cohort [in Italian].

[Ferrante et al. \(2007\)](#) examined cancer mortality in a cohort consisting of family members of men who had been employed in the asbestos-cement factory in Casale Monferrato, Italy, described in the preceding paragraph. Exposure was to a mix of crocidolite and chrysotile. Among women with domestic exposure to asbestos, 11 deaths from ovarian cancer were observed versus 7.7 expected (SMR, 1.42; 95%CI: 0.71–2.54).

[Germani et al. \(1999\)](#) examined mortality from ovarian cancer in a cohort of 631 women workers in Italy who had been compensated for asbestosis. The type of fibre to which the women were exposed was not specified. In the total cohort, there were nine deaths from ovarian cancer (SMR, 4.77; 95%CI: 2.18–9.06). In the subset of women from the asbestos-textile industry, there were four deaths from ovarian cancer (SMR, 5.26; 95%CI: 1.43–13.47). In the subcohort from the asbestos cement industry, there were five deaths from ovarian cancer (SMR = 5.40; 95%CI: 1.75 – 12.61).

[Rösler et al. \(1994\)](#) examined cancer mortality in a cohort of 616 women workers in Germany who had been occupationally exposed to asbestos. Proportionate mortality was computed according to cause of death. A total of 95% of the asbestos used in Germany at this time was chrysotile, but the authors state that “admixture of crocidolite cannot be excluded, particularly in the manufacture of asbestos textile.” Two deaths

from ovarian cancer were observed versus 1.8 expected (SMR, 1.09; 95%CI: 0.13–3.95).

(i) *Population-based cohort studies*

[Vasama-Neuvonen et al. \(1999\)](#) conducted a case-control study of ovarian cancer of occupational exposures in Finland. The asbestos fibre type was not specified and the standardized incidence ratio was 1.30 (95%CI: 0.9–1.80) between ovarian cancer and exposure to “high levels of asbestos.”

[Pukkala et al. \(2009\)](#) examined the incidence of ovarian cancer among women employed in various occupational categories in Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Among the groups examined were plumbers, a group with known occupational exposure to asbestos. Fibre type was not specified. A total of four ovarian cancers were observed in these women plumbers. The standardized incidence ratio was 3.33 (95%CI: 0.91–8.52)

(b) *Case-control studies*

[Langseth & Kjærheim \(2004\)](#) conducted a nested case-control study to examine the association between asbestos exposure and ovarian cancer within a cohort of female pulp and paper workers in Norway that had previously been found to have excess mortality from ovarian cancer (37 ovarian cancers observed versus 24 expected; SIR, 1.50; 95%CI: 1.07–2.09). The asbestos fibre type was not specified. In the case-control study, the odds ratio for occupational exposure to asbestos, based on 46 cases of ovarian cancer, was 2.02 (95%CI: 0.72–5.66).

2.5 Synthesis

The Working Group noted that a causal association between exposure to asbestos and cancer of the larynx was clearly established, based on the fairly consistent findings of both the occupational cohort studies as well as the case-controlcase-control studies, plus the evidence for positive

exposure-response relationships between cumulative asbestos exposure and laryngeal cancer-cancer of the larynx reported in several of the well-conducted cohort studies. This conclusion was further supported by the meta-analyses of 29 cohort studies encompassing 35 populations and of 15 case-controlcase-control studies of asbestos exposure and laryngeal cancer-cancer of the larynx undertaken by the [IOM \(2006\)](#). However, there is insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause laryngeal cancer-cancer of the larynx.

The Working Group noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos ([Acheson et al., 1982](#); [Wignall & Fox, 1982](#); [Germani et al., 1999](#); [Berry et al., 2000](#); [Magnani et al., 2008](#)). The conclusion received additional support from studies showing that women and girls with environmental, but not occupational exposure to asbestos ([Ferrante et al., 2007](#); [Reid et al., 2008, 2009](#)) had positive, though non-significant, increases in both ovarian cancer incidence and mortality.

The Working Group carefully considered the possibility that cases of peritoneal mesothelioma may have been misdiagnosed as ovarian cancer, and that these contributed to observed excesses. Contravening that possibility is the finding that three of the studies cited here specifically examined the possibility that there were misdiagnosed cases of peritoneal mesothelioma, and all failed to find sufficient numbers of misclassified cases. The Working Group noted that the possibility of diagnostic misclassification had probably diminished in recent years because of the development of new immunohistochemical diagnostic techniques.

The conclusion of the Working Group received modest support from the findings of

non-significant associations between asbestos exposure and ovarian cancer in two case-control studies ([Vasama-Neuvonen et al., 1999](#); [Langseth & Kjærheim, 2004](#)).

And lastly, the finding is consistent with laboratory studies documenting that asbestos can accumulate in the ovaries of women with household exposure to asbestos ([Heller et al., 1996](#)) or with occupational exposure to asbestos ([Langseth et al., 2007](#)).

The study by [Heller et al. \(1996\)](#) was a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure. The study found “significant asbestos fibre burdens” in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight). By contrast, only one of the 17 women without household exposure had counts in that range.

The study by [Langseth et al. \(2007\)](#) found approximately $3\text{--}4 \times 10^5$ asbestos fibres per gram (net weight) in normal ovarian tissue taken from 2/46 patients with ovarian adenocarcinoma. It is unclear how many of these fibres were verified as asbestos because it is stated in the publication that three chrysotile and one crocidolite asbestos fibres were identified in Case 1, and two anthophyllite and one chrysotile fibre were identified in Case 2. This small number of confirmed asbestos fibres in only two of the patients could be due to sample contamination. Technical caveats associated with quantification of asbestos fibre tissue burdens are discussed in Section 4 of this *Monograph* and in [IOM \(2006\)](#).

Further discussion of the biological plausibility of an association between asbestos exposure and ovarian cancer is to be found in Section 4 of this *Monograph*.

The Working Group noted a positive association between exposure to asbestos and cancer of

the pharynx, based on the fairly consistent positive findings in a series of well conducted cohort studies of populations occupationally exposed to asbestos ([Selikoff & Seidman, 1991](#); [Sluis-Cremer et al., 1992](#); [Reid et al., 2004](#); [Pira et al., 2005](#)) as well as on the positive findings of three case-control studies ([Zheng et al., 1992](#); [Marchand et al., 2000](#); [Berrino et al., 2003](#)). This conclusion was further supported by the findings of the meta-analysis conducted by the IOM. While tobacco smoking and alcohol consumption are clearly the dominant risk factors for cancer of the pharynx in industrialized countries, these associations between cancer of the pharynx and asbestos remained evident in several studies when tobacco and alcohol exposures were considered. The Working Group observed that the strongest associations between asbestos exposure and cancer of the pharynx were seen in studies that specifically examined cancer of the hypopharynx, the portion of the pharynx that is located closest to the larynx. However, there is insufficient information in the published literature to discern whether there are any differences among asbestos fibre types in their ability to cause cancer of the pharynx.

The Working Group noted a positive association between exposure to asbestos and cancer of the stomach, based on the positive associations between asbestos exposure and death from stomach cancer observed in several of the cohort studies with heaviest asbestos exposure ([Selikoff et al., 1964](#); [Enterline et al., 1987](#); [Raffn et al., 1989](#); [Liddell et al., 1997](#); [Musk et al., 2008](#)). The conclusion was further supported by the positive dose-response relationships observed between cumulative asbestos exposure and stomach cancer mortality in several cohort studies ([Selikoff & Hammond., 1979](#); [Zhang & Wang, 1984](#); [Liddell et al., 1997](#); [Pang et al., 1997](#)). It was supported by the results of two large and well performed meta-analyses ([Frumkin & Berlin, 1988](#); [Gamble, 2008](#)). It received borderline support from the IOM meta-analysis of cohort

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studies, and also from the IOM meta-analysis of case-control studies, which show an especially strong relationship when only extreme exposures are considered. It was supported by the comparison developed by the Working Group between standardized incidence ratios for lung cancer and stomach cancer.

Positive associations between asbestos exposure and stomach cancer and positive dose-response relationships are most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and stomach cancer, even if such an association were truly present.

[The Working Group noted that heavy occupational exposure to dust, as had likely occurred in the case of the Quebec asbestos cohort, could have been an effect modifier. Low socioeconomic status is also a potential confounder.]

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause stomach cancer. In the study by [Liddell et al. \(1997\)](#) exposure was to virtually pure chrysotile asbestos, in the study by [Musk et al. \(2008\)](#) the exposure was predominantly to crocidolite, and in most of the other published studies that observed positive associations, populations were exposed to mixtures of different asbestos fibres.

The Working Group noted a positive association between exposure to asbestos and cancer of the colorectum, based on the fairly consistent findings of the occupational cohort studies, plus the evidence for positive exposure-response relationships between cumulative asbestos exposure and cancer of the colorectum consistently reported in the more detailed cohort studies

([McDonald et al., 1980](#); [Albin et al., 1990](#); [Berry et al., 2000](#); [Aliyu et al., 2005](#)). The conclusion was further supported by the results of four large and well performed meta-analyses ([Frumkin & Berlin 1988](#); [Homa et al., 1994](#); [IOM, 2006](#); [Gamble, 2008](#)).

Positive exposure-response relationships between asbestos exposure and cancer of the colorectum appear most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and cancer of the colorectum, even if such an association were truly present.

The apparently non-positive findings of several of the case-control studies are not a deterrent to this conclusion. The majority of these case-control studies incorporated relatively little information on levels of asbestos exposure; indeed, most of them considered exposure as simply a dichotomous yes/no variable. Some of the case-control studies also may be compromised by inadequate duration of follow-up. Thus, the Garabrant study ([Garabrant et al., 1992](#)) may be subject to the criticism, offered by [Gerhardsson de Verdier et al. \(1992\)](#) that “the highest duration of exposure...was ‘at least 15 years,’ a period that may be too short to detect an elevated risk.”

There is some suggestion in the literature that the association between asbestos might be stronger for colon cancer than for rectal cancer. This view is supported by the meta-analysis of [Gamble \(2008\)](#) which found a positive dose-response relationship for cancer of the colorectum taken together, but not for rectal cancer. It is supported also by the study of [Jakobsson et al. \(1994\)](#), which found excess of cancer of the right colon in asbestos-exposed workers, but not of the left colon.

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause cancer of the colorectum. It is of note in the study by [McDonald et al. \(1980\)](#) that exposure was to virtually pure chrysotile asbestos, whereas in most of the other studies cited above, populations were exposed to mixtures of different asbestos fibres.

3. Cancer in Experimental Animals

3.1 Introduction

Asbestos is a collective name for six different types of fibres: chrysotile, crocidolite, amosite, anthophyllite, tremolite, actinolite (see Section 1). Dusts from various deposits of the same type of asbestos can cause variations in the severity of the effects observed. Erionite is a fibrous zeolite found in Central Anatolia (Turkey), and Oregon (USA) (see Section 1 of the *Monograph* on Erionite). Talc is a hydrated magnesium silicate, and talc ore may contain several other minerals including anthophyllite, tremolite, calcite, dolomite, magnesite, antigorite, quartz, pyrophyllite micas, or chlorites (see Section 1).

The definition of pathogenic fibre properties as “sufficiently long, thin, and durable” is the subject of much debate, as are the differences between the exposure–response relationships or retained dose–response relationships of asbestos fibres in man and in rats, and the potential differences in the carcinogenicity of chrysotile compared to the various amphibole asbestos types. One of the reasons for a potential difference is a difference in the biopersistence between the two asbestos groups mentioned. The biopersistence is higher in the amphibole group ([Hesterberg et al., 1996, 1998a, b](#)). The rat is the main test model for fibre-induced diseases. As the removal of asbestos fibres due to biosolubility is slow compared to the lifetime of rats and hamsters, experiments with

this model may not be appropriate in predicting results of risk in humans ([Berry, 1999](#)).

Critical fibre dimensions to be used in toxicology and occupational regulations were discussed by the Working Group. It is generally agreed that the carcinogenic potency of a fibre increases with fibre length. Apart from the ongoing scientific view, standards of regulated fibres, with few exceptions, are based on the WHO fibre definition: aspect ratio ≥ 3 : 1, length $\geq 5 \mu\text{m}$, diameter $\leq 3 \mu\text{m}$.

The tested materials (asbestos and erionite) are not presented in separate tables as in many cases they were tested in parallel experiments. The reason to split the inhalation studies into two tables (Table 3.1; Table 3.2) is that in many studies, various asbestos fibres were used as positive control in studies in which man-made fibres were tested (Table 3.2). In these latter studies, normally only one asbestos concentration was used. As for intrapleural and intraperitoneal studies, Table 3.4 is separate from Table 3.5 because the studies of [Stanton et al. \(1981\)](#) (see Table 3.5) included many fibre types – which also included fibres not to be reviewed here – and was designed to investigate the effect of fibre length and fibre type on mesothelioma induction.

A general evaluation on the type of fibre application in animal studies and an evaluation of some of the asbestos studies listed in Tables 3.1–3.5 can be found in [Pott \(1993\)](#) and [IARC \(2002\)](#).

3.2 Inhalation exposure

[Table 3.1](#) and [Table 3.2](#) give an overview of the numerous inhalation experiments on asbestos, and a few experiments on erionite. Some of these are described more extensively below.

Bronchial carcinomas and pleural mesotheliomas have been observed in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in

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tumour incidence at other sites. [The Working Group noted that in many studies, no complete histopathology was done.] All relatively short UICC asbestos preparations showed chronic effects in lung (based on fibre lengths $> 5 \mu\text{m}$ in the dust chamber) for fibres quantitatively roughly the same.

One of the first inhalation study with asbestos in rats that showed exposure–response relationships is the experiment of [Wagner et al. \(1974\)](#). Wistar rats were exposed to $10\text{--}15 \text{ mg/m}^3$ of one of the five UICC standard asbestos samples for 7 hours per day, mostly 5 days per week. The duration of exposure lasted from one day to 24 months. According to the reported data, in the group exposed to crocidolite for one day, lung tumours and one mesothelioma were found in 7/43 rats (16%). The corresponding exposure to chrysotile A (from Canada) resulted in lung tumours in 5/45 rats; for amosite 4/45 rats developed lung tumours and one mesothelioma. Three months of exposure to the five UICC standard asbestos samples resulted in the following thoracic tumour (mainly of the lung) incidences: chrysotile A, 44%; chrysotile B (from Zimbabwe), 53%; crocidolite, 42%; amosite, 27%; anthophyllite, 16%. Further results are listed in [Table 3.1](#). In the 126 control rats, seven animals were also found to have lung tumours ([Table 3.3](#)). This high spontaneous lung tumour rate is a unique finding in Wistar rats. A review of unexposed control groups of many other studies shows that spontaneous lung tumours are very rare in this rat strain ([Pott et al., 1995](#); [Table 3.3](#)); on average, the incidence is less than one percent. Therefore, the very high tumour incidences described in this first inhalation study of [Wagner et al. \(1974\)](#) might be a misinterpretation of histopathological lesions because of a lack of experience at that time.

In a study conducted by [Davis et al. \(1978\)](#), five groups of Wistar rats were exposed to chrysotile ($2.0, 10 \text{ mg/m}^3$), crocidolite ($5.0, 10 \text{ mg/m}^3$), or amosite (10 mg/m^3). The highest

tumour incidences (21–38%) were found in the chrysotile-exposed animals. This may be due to the relatively high fraction of fibres longer than $20 \mu\text{m}$ in the chrysotile dust used in this experiment. In addition to the lung tumours, extrapulmonary neoplasms included a relatively large number of peritoneal connective tissue tumours.

In a further study by [Davis et al. \(1986b\)](#), inhalation of short-fibred amosite did not produce tumours in Wistar rats (0/42). In contrast, there was a tumour incidence of 13/40 (33%) in a group exposed to long-fibred amosite. [The Working Group noted that extensive milling to produce short fibres may have altered the surface reactivity, see Section 4].

A group of 48 SPF Fischer rats was exposed to 10 mg/m^3 UICC chrysotile B by inhalation for 7 hours per day, 5 days per week, for 12 months ([Wagner et al., 1984b](#)). This group served as positive controls in a study in which various man-made fibres were tested. After exposure, the animals were kept until natural death. Twelve thoracic tumours (one adenoma, 11 adenocarcinomas) were observed in 48 rats. In the untreated control group, no lung tumours were observed in 48 rats.

[Smith et al. \(1987\)](#) exposed groups of 58 female Osborne-Mendel rats to 7 mg/m^3 UICC crocidolite asbestos for 6 hours per day, for 5 days per week, for 2 years. After this treatment, rats were observed for life. The tumour incidence in rats exposed to crocidolite was 3/57 (one mesothelioma and two carcinomas). In the control group, no tumours were observed in 184 rats.

Special attention should be drawn to the crocidolite study with male Fischer rats of [McConnell et al. \(1994\)](#) because this study is very well documented. The exposure to 10 mg dust/m^3 (with 1610 WHO fibres/mL containing 236 fibres $> 20 \mu\text{m}$) for 6 h per day, 5 days per week had to be stopped after 10 months because of unexpected mortality, which was interpreted as a sign that the maximum tolerated dose had been exceeded. The number of WHO fibres per μg dry

Table 3.1 Studies of cancer in experimental animals exposed to various asbestos species and erionite (inhalation exposure)^a

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours ^b / No. of animals examined	% tumours	Comments	Reference
Asbestos									
Chrysotile, Canada	86	NR	White rats 16 months or longer	6 h/d 5 d/wk 62 wk	0	10/41 ^c	24		Gross et al. (1967)
	50	1105	Sprague- Dawley rats lifetime	4 h/d 4 d/w 24 mo	0	5/46	11		Reeves et al. (1974)
Chrysotile UICC/A	14.7	NR	Wistar rats lifetime	7 h/d 1 d	0	5/45	11		Wagner et al. (1974)
	12.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	16/36	44		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	8/19	42		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	19/27	70		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	11/17	65		

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Table 3.1 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours ^{b/} No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/B	9.7	NR	Wistar rats lifetime	7 h/d 1 d	0	1/42	2		
	12.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	18/34	53		
	10.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	5/17	29		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	3	14/23	61		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	11/21	52		
Crocidolite UICC	12.5	NR	Wistar rats lifetime	7 h/d 1 d	1	7/43	16		
	12.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	1	15/36	42		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	4/18	22		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/26	77		
	10.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/18	72		

Table 3.1 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours ^{b/} No. of animals examined	% tumours	Comments	Reference
Amosite UICC	14.1	NR	Wistar rats lifetime	7 h/d 1 d	1	4/45	9		
	12.4	NR	Wistar rats lifetime	7 h/d 5 d/wk	0	10/37	27		
	11.2	NR	Wistar rats lifetime	3 mo 7 h/d 5 d/wk	0	2/18	11		
	10.8	NR	Wistar rats lifetime	6 mo 7 h/d 5 d/wk	0	10/25	40		
	10.6	NR	Wistar rats lifetime	12 mo 7 h/d 5 d/wk	0	13/21	62		
Anthophyllite UICC	12.8	NR	Wistar rats lifetime	7 h/d 1 d	0	2/44	5		
	13.5	NR	Wistar rats lifetime	7 h/d 5 d/wk	0	6/37	16		
	10.9	NR	Wistar rats lifetime	3 mo 7 h/d 5 d/wk	0	6/18	33		
	11.4	NR	Wistar rats lifetime	6 mo 7 h/d 5 d/wk	1	21/28	75		
	10.6	NR	Wistar rats lifetime	12 mo 7 h/d 5 d/wk	1	17/18	94		
Amosite UICC	10	550	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/43	5		Davis et al. (1978)

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Table 3.1 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours/ No. of animals examined	% tumours	Comments	Reference
Crocidolite UICC	5	430	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	3/43	7		
	10	860	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	1/40	3		
Chrysotile SFA	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	1	1/40	3		Wagner et al. (1980)
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	4/18	22		
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	8/22	36		
Chrysotile grade 7	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	1/39	3		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	5/18	28		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	3/24	13		
Chrysotile UICC (B)	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	4/40	10		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	10/18	56		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	6/23	26		

Asbestos

Table 3.1 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma animals	No. of animals with thoracic tumours ^{b/} No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC /A	2	390	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	9/42	21		Davis et al. (1978)
Chrysotile UICC /A	10	1950	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/40	38		
Chrysotile UICC	9	NR	Wistar rats lifetime	7 h/d 1 d/wk 12 mo	0	6/43	14	Peak dosing (one d/wk); no control group	Davis et al. (1980a)
Amosite UICC	50	NR	Wistar rats lifetime	7 h/d 1 d/w 12 mo	0	6/44	14	Peak dosing (one d/wk); no control group	
Chrysotile UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/43 (8 malignant, 7 benign)	35	No control group	Davis et al. (1980b)
Chrysotile "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	11/42 (3 malignant, 8 benign)	26	No control group	
Amosite "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/37	0	No control group	
Amosite UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/40	5	No control group	
Tremolite	10	1600	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/39	51		Davis et al. (1985)
Crocidolite UICC	10	1630/350 ^d	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	1/28	4		Wagner et al. (1985)
Chrysotile WDC textile yarn	3.5	679	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	18/41	44		Davis et al. (1986a)

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Table 3.1 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours/ No. of animals examined	% tumours	Comments	Reference
Chrysotile factory WDC	3.7	468	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	21/44	48		
Chrysotile textile yarn	3.5	428	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	16/42	38		
Chrysotile experimental WDC	3.5	108	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	4	21/43	49		
Chrysotile experimental WDC reversed daylight	3.8	111	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	18/37	49		
Amosite “long”	10	2060/1110 ^d	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	13/40	33		Davis et al. (1986b)
Amosite “short”	10	70/12 ^d	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/42	0		
Crocidolite UICC	10	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	1/28	4		Wagner et al. (1987)
Chrysotile, Canada, “long”	10	5510/1930 ^d	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	22/40	55	1 peritoneal mesothelioma was observed in addition	Davis & Jones (1988)
Chrysotile, Canada, “short”	10	1170/330 ^d	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	7/40	18	1 peritoneal mesothelioma was observed in addition	
Chrysotile UICC/A “discharged”	10	2670	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	11/39	28		Davis et al. (1988)

Asbestos

Table 3.1 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma animals	No. of animals with thoracic tumours ^{b/} No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	14/36	39		
Chrysotile UICC/A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	13/37	35		Davis et al. (1991a)
Chrysotile UICC/A	10	2545	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	26/41	63	Increase of tumour rate by particulate dust	
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile UICC/A	10	1960	Wistar rats lifetime	5 h/d 5 d/w 12 mo	6	22/38	58	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	3648	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	20/40	50	Increase of tumour rate by particulate dust	Davis et al. (1991a)
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	4150	Wistar rats lifetime	5 h/d 5 d/w 12 mo	8	26/39	67	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile Jeffrey	11	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	20/52	38		Mc Connell et al. (1991)

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Table 3.1 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours ^{b/} No. of animals examined	% tumours	Comments	Reference
Chrysotile	NR	NR	Baboons 6 yr	6 h/d 5 d/wk 4 years	0	0/6 ^e	0		Goldstein & Coetzee (1990)
Crocidolite UICC	12-14	1130-1400	Baboons 6 yr	6 h/d 5 d/wk 4 yr	3	3/21 ^f	14		
Amosite UICC	7	1110	Baboons 6 yr	6 h/d 5 d/wk 4 yr	2	2/11 ^f	18		Goldstein & Coetzee (1990), Webster <i>et al.</i> (1993)
Erionite									
Erionite, Oregon	10	354	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	27	27/28	96		Wagner <i>et al.</i> (1985)
Erionite, Oregon	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	24	24/27	89	No control group	Wagner (1990)
Erionite, Oregon "short"	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	0/24	0	No control group	

^a negative control groups: see Table 3.3^b Animals with benign or malignant lung tumour or pleural mesothelioma. The percentage of animals with tumours is related to the number of rats examined which were alive at a certain point in time (e.g. at the beginning of the experiment or after one year, or at the point in time of the death of the first animal with a tumour). Often, this is not clearly specified.^c observation time ≥ 6 mo^d Fibre count refers to fibres with lengths > 10 µm and diameters < 1 µm, in the aerosol^e observation time ≥ 4 yr^f observation time ≥ 5 yr^{d, e} day or days; h, hour or hours; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

From Pott & Roller (1993b)

Table 3.2 Studies of cancer in experimental animals in which asbestos was used as positive control group (in inhalation studies of various man-made mineral fibres)

Test substance	Concentration (mg/m ³)	Aerosol fibres per cm ³ (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours ^a / No. of animals	% tumours	Comments	Reference
Amosite	NR	981 89 f > 20 µm/ cm ³	AF/HAN rats, 24 mo	7 h/d 5 d/wk 12 mo	2	18/42 (7 carcinomas, 9 adenomas)	43		Davis et al. (1996) , Cullen et al. (2000)
Chrysotile UICC/B	10	NR	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	11/56 (7 adenocarcinomas, 4 adenomas)	20		McConnell et al. (1984)
Chrysotile UICC/B	10	3832/1513 ^b	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	12/48 (11 adenocarcinomas, 1 adenoma)	25		Wagner et al. (1984b)
Chrysotile NIEHS, Canada	10	10 600	Fischer rats, 24 mo	6 h/d 5 d/wk 24 mo	1	14/69	20		Hesterberg et al. (1993)
Crocidolite	10	1610	Fischer 344/N rats, 24 mo	6 h/d 5 d/wk 10 mo	1	14/106 (10 adenomas, 5 carcinomas)	13		McConnell et al. (1994)
Crocidolite UICC	7	3000/90 ^b	Osborne-Mendel rats, lifetime	6 h/d 5 d/wk 24 mo	1	3/57 (1 mesothelioma, 2 carcinomas)	5		Smith et al. (1987)
Chrysotile UICC/A	Cumulative dose: 13 800 mg.h/m ³	NR	Rats, lifetime	6 h/d 5 d/wk 18 mo	0	9/39 (5 adenomas, 1 adenocarcinoma, 3 squamous cell carcinomas)	23	Strain not specified	Pigott & Ishmael (1982)
Amosite UICC	300	3090	Sprague-Dawley rats, 18-24 mo	6 h/d 5 d/wk 3 mo	0	3/16 ^c	19	Small number of animals; D= 0.4 µm	Lee et al. (1981) , Lee & Reinhardt (1984)
Chrysotile, Canada	5	5901	Wistar rats, 24 mo	5 h/d 5 d/wk 12-24 mo	0	9/47	19		Le Bouffant et al. (1987)
Chrysotile Calidria	6	131	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	0/50	0		Muhle et al. (1987)

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Table 3.2 (continued)

Test substance	Concentration (mg/m ³)	Aerosol fibres per cm ³ (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours ^a / No. of animals	% tumours	Comments	Reference
Crocidolite, South Africa	2.2	162	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	1/50	2		Muhle et al. (1987)
Amosite UICC	300	3090	Syrian golden hamsters, 18–24 mo	6 h/d 5 d/wk 3 mo	0	0/12	0	Small number of animals diameter, 0.4 µm	Lee et al. (1981) , Lee & Reinhardt (1984)
Crocidolite UICC	7	3000/90 ^b	Syrian golden hamsters, lifetime	6 h/d 5 d/wk 24 mo	0	0/58	0		Smith et al. (1987)
Amosite	0.8	36 WHO f/cm ³ 10 f > 20 µm/cm ³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	3	3/83	3.6		McConnell et al. (1999)
	3.7	165 WHO f/cm ³ 38 f > 20 µm/cm ³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	22	22/85	26		
	7.1	263 WHO f/cm ³ 69 f > 20 µm/cm ³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	17	17/87	20		
Crocidolite UICC	13.5	1128	Baboons lifetime	7 h/d 5 d/wk 40 mo	0	0/10	0	All males	Goldstein et al. (1983)

^a n = animals with benign or malignant lung tumour or pleural mesothelioma^b Number of fibres with a length > 10 µm and a diameter < 1 µm in the aerosold, day or days; f, fibre; h, hour or hours; mo, month or months; NR, not reported; RCF, refractory ceramic fibre; wk, week or weeks
From [Pott & Roller \(1993b\)](#)

Table 3.3 Negative controls (clean air for lifetime) in carcinogenicity studies after inhalation exposures from [Table 3.1](#) and [Table 3.2](#)

Species and strain	Number of pleural mesothelioma	No. of animals with thoracic tumours ^a / No. of animals	Reference
Fischer rats	0	0/48	Wagner et al (1984b)
Fischer rats	0	0/28	Wagner et al. (1985)
Fischer rats	0	0/28	Wagner et al. (1987)
Fischer rats	0	1/56	McConnell et al. (1991)
Fischer rats	0	4/123	Hesterberg et al. (1993)
Fischer rats	0	2/126	McConnell et al. (1994)
Osborne-Mendel rats	0	0/184	Smith et al. (1987)
Sprague-Dawley rats	0	1/5	Reeves et al. (1974)
Sprague-Dawley rats	0	0/19	Lee et al. (1981)
White rats	0	0/25	Gross et al. (1967)
Wistar rats	0	7/126	Wagner et al. (1974)
Wistar rats	0	0/20	Davis et al. (1978)
Wistar rats	0	1/71	Wagner et al. (1980)
Wistar rats	0	0/36	Davis et al. (1985)
Wistar rats	0	2/39	Davis et al. (1986a)
Wistar rats	0	0/25	Davis et al. (1986a)
Wistar rats	0	0/110	Muhle et al. (1987)
Wistar rats	0	2/36	Davis et al. (1988)
Wistar rats	0	0/25	Davis et al. (1988)
Wistar rats	0	2/47	Davis & Jones (1988)
Wistar rats	0	2/47	Davis et al. (1991a)
Syrian golden hamsters	0	1/170	Smith et al. (1987)
Syrian golden hamsters	0	0/83	McConnell et al. (1999)

^a n = animals with benign or malignant lung tumour or pleural mesothelioma

lung tissue was 1850 (73 fibres > 20 µm) at the end of exposure and 759 WHO fibres (41 fibres > 20 µm) 12 months later. Fourteen out of 106 rats (13.2%), which survived the second year or longer, died with lung tumour (five of these rats developed lung carcinomas), and one rat also developed a mesothelioma. In the control group, 2/126 rats developed lung adenomas.

In two lifetime studies, male and female Fischer rats were exposed to either 10 mg/m³ erionite ([Wagner et al., 1985](#)) or an unknown concentration of erionite ([Wagner, 1990](#)) for 6 hours per day, 5 days per week, for 12 months. Twenty seven out of 28 rats, and 24/27 rats developed pleural mesotheliomas, respectively. No lung tumours were observed. [The Working

Group noted the lack of control group in the study by [Wagner \(1990\)](#).]

[McConnell et al. \(1999\)](#) exposed three groups of 125 male Syrian golden hamsters to 0.8, 3.7 and 7.1 mg/m³ amosite for 6 hours per day, 5 days per week, for 78 weeks. They were then held unexposed for 6 weeks. Among animals that survived for at least 32 weeks, 3/83, 22/85 and 17/87 developed pleural mesotheliomas, respectively. No mesotheliomas were observed in 83 untreated controls and no lung tumours were observed in any groups.

Some experiments were reported with baboons. After amosite exposure and crocidolite exposure for 4 years, 2/11 baboons and 3/21 baboons developed pleural mesothelioma,

respectively ([Goldstein & Coetzee, 1990](#); [Webster et al., 1993](#)).

3.3 Intrapleural and intraperitoneal administration

Animal experiments had shown that an intrapleural injection of a suspension of asbestos dusts in rats leads to mesotheliomas ([Wagner, 1962](#); [Wagner & Berry, 1969](#)). The serosa has subsequently been taken as a model for the examination of the carcinogenicity of fibrous dusts in numerous studies. Some groups have opted for administration into the pleural cavity, others preferring intraperitoneal injection of dust suspensions. In comparison with the intrapleural model, the intraperitoneal carcinogenicity test on fibres has proven to be the method with the far greater capacity and, consequently, the greater sensitivity (see also [Pott & Roller, 1993a](#)). Results from these numerous experiments using asbestos and erionite are listed in [Table 3.4](#).

[Table 3.5](#) contains a summary of the experiments by [Stanton et al. \(1981\)](#). In this extensive study, the authors implanted 72 dusts containing fibres of various sizes in the pleura of Osborne-Mendel rats. The probability of the development of pleural mesotheliomas was highest for fibres with a diameter of less than 0.25 µm and lengths greater than 8 µm.

In summary, samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelioma induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

3.4 Intratracheal administration

Only a few studies have been carried out with intratracheal instillation of asbestos fibres in rats ([Pott et al., 1987](#); [Smith et al., 1987](#)), and hamsters

([Pott et al., 1984](#); [Feron et al., 1985](#); [Smith et al., 1987](#)). Principally, in this experimental model, asbestos fibres induced lung tumours in rats, and lung tumours and mesotheliomas in hamsters. Studies in hamsters are described below.

In a 2-year study, a group of male Syrian golden hamsters [initial number unspecified] was intratracheally instilled with 1 mg UICC crocidolite in 0.15 mL saline once a week for 8 weeks. At the end of the experiment, the incidences of lung carcinomas and of pleural mesotheliomas were 9/142 [$P < 0.01$] and 8/142 [$P < 0.01$], respectively. No thoracic tumours were observed in 135 titanium-dioxide-treated control animals ([Pott et al., 1984](#)).

In a lifetime study, a group of Syrian golden hamsters [sex and initial number unspecified] was intratracheally instilled with 2 mg UICC crocidolite in 0.2 mL saline once a week for 5 weeks. At the end of the experiment, 20/27 animals developed broncho-alveolar tumours ($p < 0.05$), including 7/27 with malignant tumours [$p < 0.05$]. No broncho-alveolar tumours were observed in 24 saline-treated controls ([Smith et al., 1987](#)).

3.5 Oral administration

A study on the carcinogenicity of ingested asbestos fibres involved male F344 rats groups exposed to amosite or chrysotile in combination with subcutaneous administration of a known intestinal carcinogen, azoxymethane (10 weekly injections of 7.4 mg/kg body weight). Fibres were administered three times a week for 10 weeks by intragastric bolus dosing (10 mg in 1 mL saline). The first experiment in this study included a full set of appropriate control groups. The experiment was terminated at 34 weeks. Neither amosite nor UICC chrysotile B, in combination with azoxymethane, increased the incidence of any intestinal tumours (≈10%) above that produced by azoxymethane alone, but the combination with either fibre type produced 4–5-fold increases

(not significant, $P > 0.1$) in metastatic intestinal tumours. A second experiment with larger groups, the same dosing regimen, and for lifetime, but with a more limited design, tested only amosite in combination with azoxymethane versus azoxymethane. Amosite did not enhance azoxymethane-induced intestinal tumours (incidence, 77% versus 67%) ([Ward et al., 1980](#); [IOM, 2006](#)). [The Working Group noted that the lack of untreated vehicle controls in the second experiment made interpretation of the results difficult considering that, compared to historical controls, there was a non-significant increase in intestinal tumours in rats exposed only to amosite ($\approx 33\%$). One cannot know whether the results observed were associated with the asbestos or with irritation from the procedure, although one would not anticipate that gavage itself would impact the lower portion of the gastrointestinal tract.]

The most definitive animal studies of oral exposure to asbestos were a series of lifetime studies conducted by the National Toxicology Program ([NTP, 1983, 1985, 1988, 1990a, b](#)), in which asbestos (chrysotile, crocidolite, and amosite) was administered in the feed of rats and hamsters. Nonfibrous tremolite was also tested in rats according to the same protocol ([NTP, 1990c](#)). Exposure of dams of the study animals (1% in the diet) was followed by exposure of the pups by gavage (0.47 mg/g water) while they were nursing, and then in the diet for the remainder of their lives: they were exposed to asbestos at the level of 1%, which was estimated by the investigators to be about 70000 times the greatest possible human exposure in drinking-water. Histopathological examination of the entire colorectum was performed. No increases in the incidence of gastrointestinal lesions (inflammatory, preneoplastic, or neoplastic) were found after exposure to intermediate-length chrysotile (from Quebec) in hamsters, to short chrysotile (from New Idria) in rats or hamsters, to amosite in rats or hamsters, to crocidolite in rats, or to non-fibrous tremolite in rats. The mesentery was

examined in detail, as well as mesenteric lymph nodes and sections of the larynx, trachea, and lungs from every animal. No lesions were found in any of those tissues. The only finding of note in the gastrointestinal tract was a slight increase in the incidence of adenomatous polyps in the large intestine after exposure to the intermediate-length chrysotile (from Quebec) in male rats (9/250 versus 0/85, $P = 0.08$), but preneoplastic changes in the epithelium were not found ([NTP, 1985](#); [IOM, 2006](#)).

3.6 Intra gastric administration

White rats, 2–3 months old, were surgically applied, on the greater curvature of the stomach, a perforated capsule containing 0 (control) or 100 mg chrysotile asbestos in a filler (beef fat: natural wax, 1:1). Tumours observed in 18/75 asbestos-exposed rats, between 18–30 months after the beginning of the experiment, were the following: eight gastric adenomas, two gastric adenocarcinomas, one gastric carcinoma, one cancer of the forestomach, one small intestine adenocarcinoma, two peritoneal mesotheliomas, and three abdominal lymphoreticular sarcomas. No tumours were observed in 75 control animals ([Kogan et al., 1987](#)). [The Working Group noted various unresolved questions regarding the design of this study in particular the very high dose of 100 mg.]

3.7 Studies in companion animals

Mesotheliomas were reported in pet dogs with asbestos exposure in the households of their owners. Eighteen dogs diagnosed with mesothelioma and 32 age-, breed- and gender-matched control dogs were investigated. Sixteen owners of cases and all owners of controls were interviewed. An asbestos-related occupation or hobby of a household member was significantly associated with mesothelioma observed in cases (OR,

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Table 3.4 Studies of cancer in rats exposed to asbestos fibres and erionite (intrapleural and intraperitoneal administration)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres ^a [10 ⁹]	Tumour incidence ^b		Significance ^c	Comments
					n/z	%		
Asbestos								
Wistar – Pott et al. (1989)	Actinolite	0.25	i.p.	0.1	20/36	56	***	
Wistar – Wagner et al. (1973)	Amosite UICC	20	i.pl.	NR	11/32	34	***	
Wistar – Davis et al. (1991b)	Amosite from UICC	0.01	i.p.	0.0003	4/48	8	*	
Wistar – Davis et al. (1991b)	Amosite from UICC	0.05	i.p.	0.002	8/32	25	***	
Wistar – Davis et al. (1991b)	Amosite from UICC	0.5	i.p.	0.02	15/32	47	***	
Wistar – Wagner et al. (1973)	Anthophyllite UICC	20	i.pl.	NR	8/32	25	***	
Wistar – Wagner et al. (1973)	Chrysotile UICC/A	20	i.pl.	NR	7/31	23	***	
Sprague-Dawley – Monchaux et al. (1981)	Chrysotile UICC/A	20	i.pl.	NR	14/33	42	***	
Sprague-Dawley – Wagner et al. (1984b)	Chrysotile UICC/A	20	i.pl.	19.6	6/48	13	**	
Wistar – Pigott & Ishmael (1992)	Chrysotile UICC/A	20	i.pl.	NR	7/48	15	***	
Fischer – Coffin et al. (1992)	Chrysotile UICC/A	0.5	i.pl.	0.90	118/142 ^d	78	***d	
		2		3.6		87		
		4		7.2		92		
		8		14		83		
		16		29		83		
		32		57		75		
Wistar – Wagner et al. (1973)	Chrysotile UICC/B	20	i.pl.	NR	10/32	31	***	
Wistar – Wagner et al. (1980)	Chrysotile UICC/B	20	i.pl.	NR	5/48	10	*	
Fischer – Wagner et al. (1987)	Chrysotile UICC/B	20	i.pl.	NR	19/39	49	***	
Wistar – Pott et al. (1989)	Chrysotile UICC/B	0.25	i.p.	0.2	23/34	68	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres ^a [10 ⁹]	Tumour incidence ^b		Significance ^c	Comments
					n/z	%		
Wistar – Davis et al. (1991b)	Chrysotile from UICC/A	0.01	i.p.	0.002	2/48	4	NS	
Wistar – Davis et al. (1991b)	Chrysotile from UICC/A	0.05	i.p.	0.009	12/32	38	***	
Wistar – Davis et al. (1991b)	Chrysotile from UICC/A	0.5	i.p.	0.09	26/32	81	***	
Wistar – Wagner et al. (1973)	Crocidolite UICC	20	i.p.l.	NR	19/32	59	***	
Fischer – Wagner et al. (1987)	Crocidolite UICC	20	i.p.l.	NR	34/40	85	***	
Fischer – Wagner (1990)	Crocidolite UICC	20	i.p.l.	NR	24/32	75	***	
Sprague-Dawley – Monchaux et al. (1981)	Crocidolite UICC	20	i.p.l.	NR	21/39	54	***	
Osborne-Mendel – Stanton et al. (1981)	Crocidolite UICC	40	i.p.l.	NR	14/29	48	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC	20	i.p.l.	NR	35/41	85	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 1 h	20	i.p.l.	NR	34/42	81	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 2 h	20	i.p.l.	NR	34/42	81	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 4 h	20	i.p.l.	NR	15/41	37	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 8 h	20	i.p.l.	NR	13/42	31	***	
Fischer – Coffin et al. (1992)	Crocidolite UICC	0.5	i.p.l.	0.04	65/144 ^d	29	*** ^d	
		2		0.16		13		
		4		0.32		50		
		8		0.65		67		
		16		1.3		58		
		32		2.6		54		
Wistar – Davis et al. (1991b)	Crocidolite from UICC	0.01	i.p.	0.0004	0/48	0	NS	
Wistar – Davis et al. (1991b)	Crocidolite from UICC	0.05	i.p.	0.002	8/32	25	***	

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Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres ^a [10 ⁹]	Tumour incidence ^b		Significance ^c	Comments
					n/z	%		
Wistar – Davis et al. (1991b)	Crocidolite from UICC	0.5	i.p.	0.02	10/32	31	***	
Wistar – Pott et al. (1987)	Crocidolite South Africa	0.5	i.p.	0.05	18/32	56	***	
Wistar – Roller et al. (1996)	Crocidolite A	0.5	i.p.	0.042	25/32	78	***	All females
Wistar – Roller et al. (1996)	Crocidolite A	0.5	i.p.	0.042	32/48	67	***	All females
Wistar – Roller et al. (1996)	Crocidolite C	0.5	i.p.	0.042	20/39	51	***	
Wistar – Davis et al. (1985)	Tremolite, Korea	25	i.p.	NR	27/29	93	***	
Wistar – Roller et al. (1996)	Tremolite B	3.3	i.p.	0.057	9/40	23	***	
Wistar – Roller et al. (1996)	Tremolite B	15	i.p.	0.26	30/40	75	***	
Erionite	Erionite type							
Sprague-Dawley – Pott et al. (1987)	Karain	1.25	i.p.	NR	38/53	72	***	
Sprague-Dawley – Pott et al. (1987)	Karain	5	i.p.	NR	43/53	81	***	
Sprague-Dawley – Pott et al. (1987)	Karain	20	i.p.	G	37/53	70	***	
Fischer – Wagner et al. (1985)	Karain	20	i.pl.	NR	38/40	95	***	
Fischer – Wagner et al. (1985)	Oregon	20	i.pl.	NR	40/40	100	***	
Wistar – Pott et al. (1987)	Oregon	0.5	i.p.	0.02	15/31	48	***	
Wistar – Pott et al. (1987)	Oregon	2	i.p.	0.08	28/31	90	***	
Fischer – Wagner (1990)	Oregon	20	i.pl.	NR	30/32	94	***	
Fischer – Wagner (1990)	Oregon “short”	20	i.pl.	NR	0/32	0	NS	
Wistar – Davis et al. (1991b)	Oregon	0.005	i.p.	0.00025	0/48	0	NS	
		0.01		0.0005	4/48	8	*	
		0.05		0.0025	15/32	47	***	
		0.5		0.025	26/32	81	***	
		2.5		0.125	30/32	94	***	
		5		0.25	21/24	88	***	
		10		0.5	20/24	83	***	
		25		1.25	17/18	94	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres ^a [10 ⁹]	Tumour incidence ^b		Significance	Comments
					n/z	%		
Porton – Hill et al. (1990)	Oregon	0.1	i.p.l.	NR	5/10	50	*	
		1		NR	9/10	90	***	
		10		NR	9/10	90	***	
		20		NR	8/10	80	***	
Wistar – Kleymenova et al. (1999)	Grusia mines	20	i.p.l.	NR	39/40	98	?	
Fischer – Coffin et al. (1992)	Oregon “C”	0.5	i.p.l.	NR	123/144 ^d	79	***d	
		2		NR		87		
		4		NR		83		
		8		NR		84		
		16		NR		87		
		32		NR		91		
Fischer – Coffin et al. (1992)	Oregon “W”	0.5	i.p.l.	NR	137/144 ^d	100	***d	
		2		NR		92		
		4		NR		100		
		8		NR		91		
		16		NR		96		
		32		NR		92		
Sprague-Dawley – Maltini & Minardi (1989)	“Sedimentary erionite”	25	i.p.l.	NR	35/40	88	***	
Sprague-Dawley – Maltini & Minardi (1989)	“Sedimentary erionite”	25	i.p.	NR	35/40	50	***	

^a The fibre numbers mainly refer to fibres with a length greater than 5 µm^b n/z number of animals with serosal tumour (mesothelioma/sarcoma) / number of animals examined^c calculation of the statistical significance with the Fisher exact test, one-sided: *** p < 0.001; ** p < 0.01; * p ≤ 0.05^d combined data of 6 groups

i.p., intraperitoneal; i.p.l., intraperitoneal; NS, not significant; NR, not reported

From [Pott & Roller \(1993b\)](#)

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Table 3.5 Carcinogenicity study of intrapleural application of asbestos fibres and other fibrous materials in female Osborne-Mendel rats (40 mg fibres per rat)

Fibrous dust (material)	No. of fibres ^a (x10 ⁶) L > 8 µm D < 0.25 µm	Probability of pleural sarcomas ^b	Pleural sarcoma incidence ^c	
			n/z	%
Tremolite 1	55	100	22/28	79
Tremolite 2	28	100	21/28	75
Crocidolite 1	6500	94 ± 6.0	18/27	67
Crocidolite 2	800	93 ± 6.5	17/24	71
Crocidolite 3	4100	93 ± 6.9	15/23	65
Amosite	140	93 ± 7.1	14/25	56
Crocidolite 4	5400	86 ± 9.0	15/24	63
Crocidolite 5 (UICC)	78	78 ± 10.8	14/29	48
Crocidolite 6	1600	63 ± 13.9	9/27	33
Crocidolite 7	18	56 ± 11.7	11/26	42
Crocidolite 8	< 0.3 ^d	53 ± 12.9	8/25	32
Crocidolite 9	710	33 ± 9.8	8/27	30
Crocidolite 10	49	37 ± 13.5	6/29	21
Crocidolite 11	< 0.3 ^d	19 ± 8.5	4/29	14
Crocidolite 12	220	10 ± 7.0	2/27	7
Talc 1	< 0.3 ^d	7 ± 6.9	1/26	4
Talc 3	< 0.3 ^d	4 ± 4.3	1/29	3
Talc 2	< 0.3 ^d	4 ± 3.8	1/30	3
Talc 4	< 0.3 ^d	5 ± 4.9	1/29	3
Crocidolite 13	< 0.3 ^d	0	0/29	0
Talc 5	< 0.3 ^d	0	0/30	0
Talc 6	80	0	0/30	0
Talc 7	< 0.3 ^d	0	0/29	0

^a Fibre numbers stated in original work as common logarithm.

^b Calculation taking into account the different life spans (life table method).

^c n/z = number of rats with pleural sarcomas/number of rats examined. Frequency of pleural sarcomas in female control rats: untreated, 3 animals out of 491 (0.6%); with non-carcinogenic lung implantates, 9 out of 441 (2.0%); with non-carcinogenic pleural implantates, 17 out of 615 (2.8%). [17 out of 615 against 3 out of 491, according to Fisher exact test $P < 0.01$]. All three control groups are brought together by [Stanton et al. \(1981\)](#) to 29 out of 1518 animals (1.9%); for this after application of the life table method a tumour probability of $7.7 \pm 4.2\%$ is indicated. [Without any reason being given it is concluded that the tumour probability in any one of the groups treated according to the life table method must exceed 30% to be “significantly” increased.] Significance limit for Fisher test in the case of 25 to 30 animals against 17 out of 615 control rats: approx. 12 to 13% tumour frequency. (The term “tumour frequency” is not to be equated with tumour probability according to the life table method. The “significance limit” of 30% mentioned by [Stanton et al. \(1981\)](#) refers to life table incidence or probability.

^d The de-logarithmised fibre numbers with the above mentioned definition are between 0 and 0.3.

From [Stanton et al. \(1981\)](#)

8.0; 95%CI: 1.4–45.9). Lung tissue from three dogs with mesothelioma and one dog with squamous cell carcinoma of the lung had higher level of chrysotile asbestos fibres than lung tissue from control dogs ([Glickman et al., 1983](#)).

3.8 Synthesis

Bronchial carcinomas and pleural mesotheliomas were observed in many experiments in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in tumour incidence at other sites. A special preparation of “long” crocidolite was more effective to induce lung tumours compared to the “short” UICC asbestos samples on the basis of administered dose in f/mL.

In one study in Syrian golden hamsters with three different concentrations of amosite, a significant increase in pleural mesothelioma incidence was observed, but no lung tumours were found.

After amosite exposure and crocidolite exposure by inhalation, 2/11 baboons and 3/21 baboons developed pleural mesothelioma, respectively.

In two studies in rats exposed to erionite, a significant increase in pleural mesothelioma incidence was observed. However, no lung tumours were found.

Samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelioma induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

Only a few studies have been carried out with intratracheal instillation of crocidolite in rats and hamsters. Malignant lung tumours were observed in rats, and pleural mesothelioma and malignant lung tumours were observed in hamsters.

Chrysotile, crocidolite and amosite were administered in the feed of rats and hamsters.

No increase of the incidence of gastrointestinal tumours was observed in both species.

No chronic studies with vermiculite containing asbestos fibres or talc containing asbestos fibres could be identified.

4. Other Relevant Data

4.1 Toxicokinetics, deposition, clearance, and translocation in humans

4.1.1 Aerodynamic and anatomical factors

Inhalation is the most important route of exposure to mineral fibres, and is associated with the development of non-malignant diseases of the lungs and pleura, and malignant diseases arising in the lung, larynx, and pleural and peritoneal linings ([IOM, 2006](#)). The deposition of particles and fibres in the lungs is dependent on their aerodynamic diameter, which is a function of geometry, aspect ratio ([IARC, 2002](#)), and density ([Bernstein et al., 2005](#)). Fibres can deposit by sedimentation, by impaction at bronchial bifurcations or by interception of the fibre tip with the bronchial wall. Smaller diameter fibres are likely to deposit in the alveoli ([Bernstein et al., 2005](#)).

Particles and fibres can be cleared from the nasal and tracheobronchial regions by mucociliary transport ([Lippmann et al., 1980](#)). Following deposition in the distal airways and alveoli, short fibres are removed more slowly following phagocytosis by alveolar macrophages. Fibre length is a limiting factor in macrophage-mediated clearance; fibres longer than the diameter of human alveolar macrophages (approximately 14–25 µm) are less likely to be cleared. Fibres may also interact with lung epithelial cells, penetrate into the interstitium, and translocate to the pleura and peritoneum or more distant sites. Fibres that are not efficiently cleared or altered by physicochemical process (e.g. breakage, splitting, or

chemical modification) are termed biopersistent ([Bernstein et al., 2005](#)). Chronic inhalation assays using man-made fibres in rodents have correlated fibre length and biopersistence with persistent inflammation, fibrosis, lung cancer, and malignant mesothelioma ([Bernstein et al., 2005](#)). However, there are interspecies differences in alveolar deposition of inhaled particles and fibres that must be considered when extrapolating results of rodent inhalation studies to humans ([IARC, 2002](#)).

4.1.2 Biopersistence of asbestos and erionite fibres

Asbestos fibres and ferruginous bodies (described subsequently in Section 4.3.1) can be identified and quantified by tissue digestion of lung samples obtained by biopsy or at autopsy ([Roggli, 1990](#)). A variety of commercial and non-commercial asbestos fibres have been identified in residents older than 40 years of age living in an urban area with no history of occupational asbestos exposure ([Churg & Warnock, 1980](#)). These and other studies confirm that asbestos fibres are biopersistent and accumulate in lung tissue as well as lymph nodes ([Dodson et al., 1990](#); [Dodson & Atkinson, 2006](#)). Asbestos fibres have also been identified in the pleura following autopsy ([Dodson et al., 1990](#); [Gibbs et al., 1991](#); [Suzuki & Yuen, 2001](#)) and in the parietal pleural in samples collected during thoracoscopy ([Boutin et al., 1996](#)). [Roggli et al. \(1980\)](#) also identified asbestos bodies in the larynx of asbestos workers at autopsy. Systemic translocation of asbestos fibres to distant organs has also been described in case reports; however, these reports should be evaluated with caution due to the numerous caveats in technical procedures used, comparison with an appropriate control population, and cross-contamination of tissue samples ([Roggli, 2006](#)). The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation

of amosite fibres deposited in the lungs has been shown in experimental animals ([Hesterberg et al., 1999](#); [Mc Connell et al., 1999](#); [IOM, 2006](#); [NIOSH, 2009](#)).

Environmental exposure to erionite fibres is associated with diffuse malignant mesothelioma in three rural villages in the Cappadocia region of Turkey ([Baris & Grandjean, 2006](#)). Lung fibre digests obtained from humans in these villages showed elevated levels of erionite fibres, and ferruginous bodies surrounding erionite fibres were found in broncho-alveolar lavage fluid ([Sébastien et al., 1984](#); [Dumortier et al., 2001](#)).

Talc particles have been found in the lungs at autopsy of both rural and urban residents as well as talc miners ([IARC, 1987b, 2010](#)). Talc particles are biopersistent in the lungs, and have been recovered in broncho-alveolar lavage fluid obtained from workers 21 years after cessation of occupational exposure ([Dumortier et al., 1989](#)). Talc contaminated with asbestos has been linked to the development of lung cancer and malignant mesothelioma ([IARC, 1987b](#)).

The association between exposure to talc, potential retrograde translocation to the ovarian epithelium, and the development of ovarian cancer is controversial ([IARC, 2010](#), and this volume).

The biological plausibility for an association between asbestos and ovarian cancer derives in part from the finding of asbestos fibres in the ovaries of women with potential for exposure to asbestos. Thus, a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure found “significant asbestos fibre burdens” in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight), but only one of the 17

women without exposure had counts in that range ([Heller et al., 1996](#)).

Further support for the biological plausibility of an association between asbestos exposure and ovarian cancer derives from an experimental study ([Graham & Graham, 1967](#)) that found that the intraperitoneal injection of tremolite asbestos into guinea-pigs and rabbits produced epithelial changes in the ovaries “similar to those seen in patients with early ovarian cancer”.

[The Working Group noted that the histopathological diagnosis of ovarian carcinoma is difficult and requires the application of immunohistochemical techniques to distinguish between this cancer and peritoneal malignant mesothelioma. These techniques and the recognition of borderline ovarian tumours and variants of serosal tumours that arise in the pelvis of women were not applied in the Graham & Graham study in 1967. In addition, mesothelial hyperplasia occurs commonly in the pelvic region, and is not considered a preneoplastic lesion ([NIOSH, 2009](#)).]

4.2 Molecular pathogenesis of human cancers related to mineral dust exposure

Cancers develop in the upper and lower respiratory tract (carcinoma of the larynx and lungs), and in the pleural and peritoneal linings (diffuse malignant mesothelioma) after a long latent period up to 20–40 years following initial exposure to asbestos or erionite fibres ([IARC, 1977](#); [IOM, 2006](#)). During the long latent period before the clinical diagnosis of cancer of the lung or of the larynx or diffuse malignant mesothelioma, multiple genetic and molecular alterations involving the activation of cell growth regulatory pathways, the mutation or amplification of oncogenes, and the inactivation of tumour-suppressor genes characterize specific histopathological types of these tumours that have

been associated with exposure to mineral dust or fibres. Some of these molecular alterations have been linked to specific chemical carcinogens in tobacco smoke ([Nelson & Kelsey, 2002](#)), and additional alterations may arise secondarily due to chronic inflammation, genetic instability, or epigenetic changes that will be discussed in detail in Section 4.3.

Additional pathways related to resistance to apoptosis, acquired genetic instability, and angiogenesis are activated or upregulated during the later stages of tumour progression of lung cancer and diffuse malignant mesothelioma ([Table 4.1](#); [Table 4.2](#)). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to asbestos fibres ([NIOSH, 2009](#)).

4.2.1 Cancer of the lung and of the larynx

Lung cancers are classified into two histological subtypes: small cell carcinoma and non-small cell carcinoma ([Table 4.1](#)). In non-small cell lung carcinoma, activating point mutations in the *K-RAS* oncogene have been linked to specific chemical carcinogens in tobacco smoke; [Nelson et al. \(1999\)](#) described more frequent *K-RAS* mutations in lung carcinomas in asbestos-exposed workers. Loss of heterozygosity and point mutations in the *p53* tumour-suppressor gene have also been linked with tobacco smoke carcinogens in cancer of the lung and of the larynx ([Pfeifer et al., 2002](#); [NIOSH, 2009](#)). These alterations have also been described in lung cancers in asbestos-exposed workers ([Nymark et al., 2008](#)).

4.2.2 Diffuse malignant mesothelioma

Malignant tumours arising in the pleural or peritoneal linings (diffuse malignant mesothelioma) have no association with tobacco smoking, and are characterized by a different spectrum of molecular alterations ([Table 4.2](#)). In contrast with lung cancers associated with tobacco smoking and asbestos exposure, mutations in the *K-RAS*

Table 4.1 Some reported molecular alterations in bronchogenic carcinoma

Functional alterations	Gene target	Histological type of lung cancer	
		Small cell	Non-small cell
Autocrine growth stimulation	Growth factors and receptors	GRP/GRP receptor SCF/KIT	TGF- α /EGFR HGF/MET
Activation of oncogenes	<i>RAS</i> mutation	<1%	15–20%
	<i>MYC</i> overexpression	15–30%	5–10%
Inactivation of tumour-suppressor genes	<i>p53</i> mutation	~90%	~50%
	<i>RB</i> mutation	~90%	15–30%
	<i>p16^{INK4A}</i> inactivation	0–10%	30–70%
	<i>FHIT</i> inactivation	~75%	50–75%
Resistance to apoptosis	<i>BCL2</i> expression	75–95%	10–35%
Genetic instability	Microsatellite instability	~35%	~22%

EGFR, epidermal growth factor receptor; FHIT, fragile histidine triad; GRP, gastrin-releasing peptide; HGF, hepatocyte growth factor; RB, retinoblastoma gene; SCF, stem cell factor; TGF- α , transforming growth factor- α .

From [Sekido et al. \(2001\)](#), [Sato et al. \(2007\)](#), [Schwartz et al. \(2007\)](#), [NIOSH \(2009\)](#)

oncogene or the *p53* tumour-suppressor gene are rare. The most frequent molecular alteration involves deletion or hypermethylation at the *CDKN2A/ARF* locus on chromosome 9p21 which contains three tumour-suppressor genes: *p15*, *p16^{INK4A}*, and *p14^{ARF}* ([Murthy & Testa, 1999](#)). Additional molecular alterations include hypermethylation and silencing of the *RASSF1A* and *GPC3* tumour-suppressor genes, and inactivation of the *NF2* tumour-suppressor gene ([Apostolou et al., 2006](#); [Murthy et al., 2000](#)).

Comparative genomic hybridization, gene expression profiling, and proteomics have been used to identify specific diagnostic and prognostic biomarkers for diffuse malignant mesothelioma ([Wali et al., 2005](#); [Greillier et al., 2008](#)). The most promising outcome of these global screening strategies is the identification of two potential serum or pleural fluid biomarkers that may provide early diagnosis of malignant pleural mesothelioma: osteopontin ([Pass et al., 2005](#)), and soluble mesothelin-related protein ([Robinson et al., 2005](#)). Both of these markers have been shown to be elevated in most patients diagnosed with diffused malignant mesothelioma, but are not entirely specific for these cancers ([Greillier et al., 2008](#)). No gene expression signature can

be attributed directly to asbestos exposure, and these studies show variable gene expression patterns resulting from limited stability of RNA, contamination of tumour samples with host cells, and use of different microarray platforms ([López-Ríos et al., 2006](#)).

In addition to the genetic and chromosomal alterations that have been identified in diffuse malignant mesothelioma ([Table 4.2](#)), epigenetic alterations characterized by altered patterns of DNA methylation have been described ([Toyooka et al., 2001](#); [Tsou et al., 2005](#)). Overall, human tumours have been characterized by global hypomethylation associated with hypermethylation of CpG islands in the promoter regions of tumour-suppressor genes leading to their inactivation. These alterations in DNA methylation are the most common molecular or genetic lesion in human cancer ([Esteller, 2005](#)). Recent comprehensive analyses of epigenetic profiles of 158 patients with malignant pleural mesotheliomas and 18 normal pleural samples using 803 cancer-related genes revealed classes of methylation profiles in malignant mesothelioma that were associated with asbestos lung burden and survival ([Christensen et al., 2009](#)). Other data confirmed hypermethylation of cell-cycle

Table 4.2 Some reported molecular alterations in diffuse malignant mesothelioma

Function	Gene target	Alteration
Autocrine growth stimulation	Growth factors and receptors	HGF/MET upregulation EGFR upregulation PDGF upregulation IGF-1 upregulation
Tumour-suppressor genes	<i>p15, p16^{INK4A}, p14^{ARF}</i>	Inactivation or deletion
	<i>Neurofibromin 2</i>	NF2 deletions, mutations
	<i>RASSF1A, GPC3</i>	Hypermethylation
Angiogenesis	VEGF	Upregulation
Apoptosis	AKT	Constitutive activation
	BCL-X	Upregulation

EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; PDGF, platelet-derived growth factor; RASSF1A, Ras-association domain family 1; VEGF, vascular endothelial growth factor

From [Murthy & Testa \(1999\)](#), [Altomare et al. \(2005\)](#), [Catalano et al. \(2005\)](#), [Kratzke & Gazdar \(2005\)](#), [Cacciotti et al. \(2006\)](#), [NIOSH \(2009\)](#)

regulatory genes as well as inflammation-associated genes and apoptosis-related genes ([Tsou et al., 2007](#); [Christensen et al., 2008](#)). [Christensen et al. \(2009\)](#) hypothesized that hypermethylation of specific genes confers a selective survival advantage to preneoplastic mesothelial cells in a microenvironment of persistent tissue injury and/or oxidative stress associated with exposure to asbestos fibres.

In summary, these new genomic and proteomics approaches offer promise for the discovery of novel biomarkers associated with the development of diffuse malignant mesothelioma following exposure to asbestos or erionite. No specific marker is yet available to identify those cancers.

4.3 Mechanisms of carcinogenesis

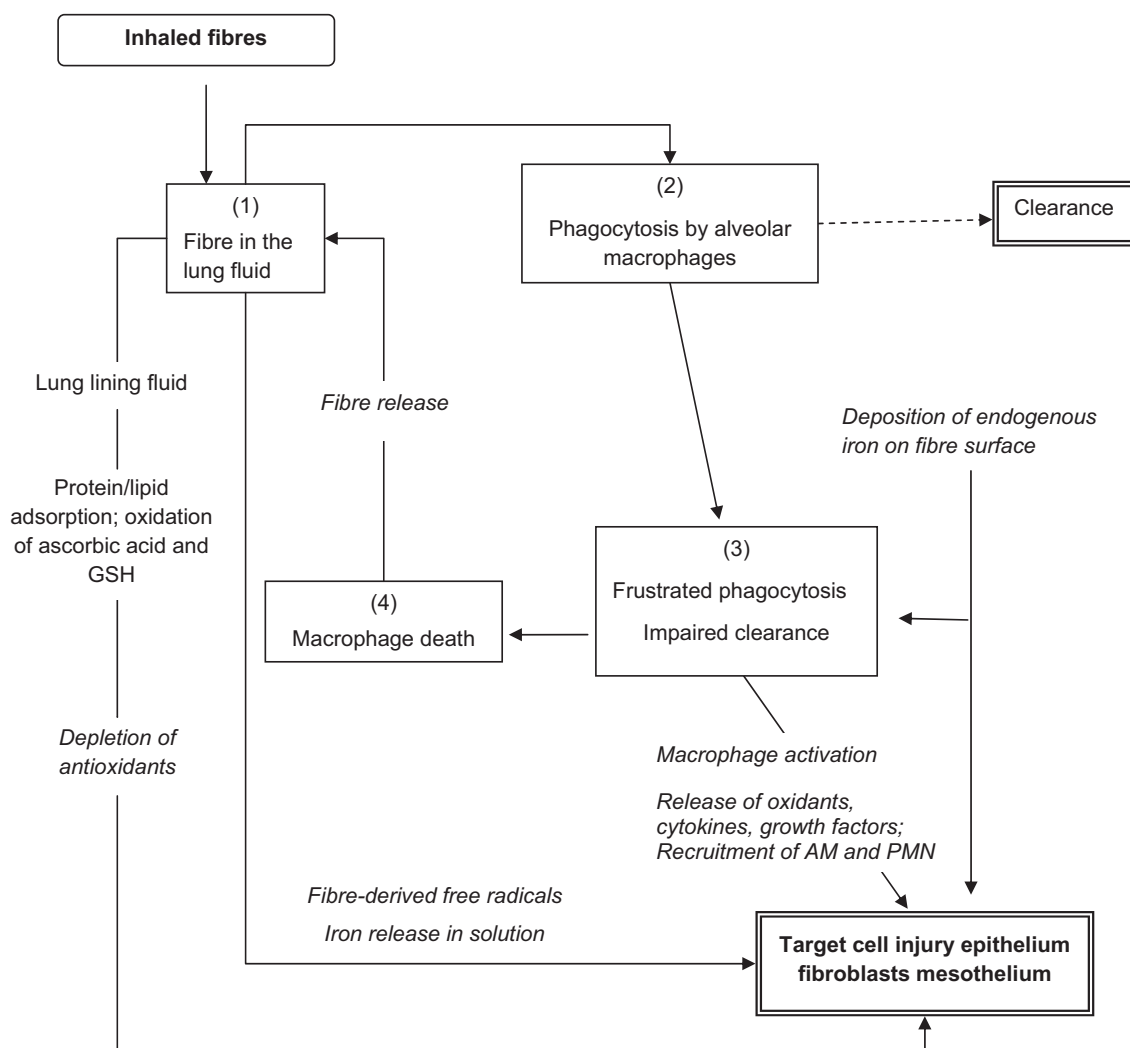
4.3.1 Physicochemical properties of mineral fibres associated with toxicity

Asbestos are natural fibrous silicates, with similar chemical composition (silica framework includes various metal cations, typically Mg^{2+} , Ca^{2+} , $Fe^{2+/3+}$, Na^{+}) mostly differing in the crystallographic constraints that yield the fibrous habit. They are poorly soluble minerals which only undergo selective leaching and incongruent dissolution. Erionite is a zeolite, which often crystallizes in thin long fibres. Major determinants of toxicity are form and size of the fibres, surface chemistry, and biopersistence. Crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, modulate surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids influence their biopersistence, a factor which modulates cumulative exposure ([Fubini, 1997](#); [Bernstein et al., 2005](#); [Fubini & Fenoglio, 2007](#); [Sanchez et al., 2009](#); Fig. 4.1).

(a) Crystal structure

Asbestos minerals can be divided into two groups: serpentine asbestos (chrysotile $[Mg_3Si_2O_5(OH)_4]$), and amphibole asbestos (crocidolite $[Na_2(Mg,Fe^{2+})_3Fe_2^{3+}Si_8O_{22}(OH)_2]$, amosite $[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]$, tremolite $[Ca_2Mg_5Si_8O_{22}(OH)_2]$, actinolite $[Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2]$, and anthophyllite $[Mg_7Si_8O_{22}(OH)_2]$). Formulae reported are ideal and are always significantly modified in nature by the occurrence of several substituting cations (e.g. $Fe^{2+/3+}$, Al^{3+} , Na^{+}). The crystal structure of chrysotile results from the association of a tetrahedral silicate sheet of composition $(Si_2O_5)_n^{2n-}$ with an octahedral brucite-like sheet of composition $[Mg_3O_2(OH)_4]_n^{2n+}$, in which iron substitutes for magnesium. The two sheets are bonded to form a 1:1 layer silicate; a slight misfit between the sheets causes curling to form

Fig. 4.1 Physicochemical properties involved in the biological activity of asbestos fibres



AMs, alveolar macrophages; GSH, glutathione; PMNs, polymorphonuclear neutrophils
Adapted from [Fubini & Otero Areán \(1999\)](#), [Fubini & Fenoglio \(2007\)](#)

concentric cylinders, with the brucite-like layer on the outside. Van der Waals interparticle forces hold together fibrils into the actual fibre so that, when chrysotile breaks up, a large number of smaller fibres or fibrils are generated ([Fubini & Otero Areán, 1999](#)).

Amphiboles have an intrinsically elongated crystal structure which breaks up along planes within the crystal structure itself into progressively smaller fragments that generally retain a fibrous aspect. This structure can be described in terms of a basic structural unit formed by a double tetrahedral chain (corner-linked SiO_4 tetrahedra) of composition $(\text{Si}_4\text{O}_{11})_n^{6n-}$. These silicate double-chains share oxygen atoms with alternate layers of edge-sharing MO_6 octahedra, where M stands for a variety of cations: mostly Na^+ , Mg^{2+} , Ca^{2+} , Fe^{2+} , or Fe^{3+} ([Fubini & Otero Areán, 1999](#)).

(b) Form and size

The pathogenic potential of asbestos depends upon its aspect ratio and fibre size. Fibre size affects respirability (respiratory zone falls off above aerodynamic diameters of $5\text{ }\mu\text{m}$) and clearance by alveolar macrophages (section 4.1.1) ([Donaldson & Tran, 2004](#)). Short fibres are cleared more efficiently than longer ones, which undergo frustrated phagocytosis by macrophages. Short amosite fibres obtained by grinding long ones are less inflammogenic ([Donaldson et al., 1992](#)), induce fewer chromosomal aberrations ([Donaldson & Golyasnya, 1995](#)), and reduce the inhibition of the pentose phosphate pathway ([Riganti et al., 2003](#)). In-vitro genotoxicity studies demonstrated that both short and intermediate chrysotile asbestos fibres induced micronuclei formation and sister chromatid exchange in Chinese hamster lung cells. Intermediate fibres were more active than short fibres even when followed by treatment with dipalmitoyl lecithin, a principal constituent of pulmonary surfactant ([Lu et al., 1994](#)). Long fibres but not short fibres of amosite asbestos,

opsonized with rat immunoglobulin, were shown to induce a dramatic enhancement of superoxide anions in macrophages isolated from rat lung ([Hill et al., 1995](#)). Asbestos bodies are formed mostly on fibres longer than $20\text{ }\mu\text{m}$ ([Roggli, 2004](#)).

The role of the aspect ratio and size appears to be different for the three major asbestos-related diseases: i) asbestosis was reported as most closely associated with the surface area of retained fibres ([NIOSH, 2009](#)) although fibrosis also correlates with fibres $> 2\text{ }\mu\text{m}$ long ([Dodson et al., 2003](#)); ii) mesothelioma is better related to the numbers of fibres longer than about $5\text{ }\mu\text{m}$ and thinner than about $0.1\text{ }\mu\text{m}$; and iii) lung cancer with fibres longer than about $10\text{ }\mu\text{m}$ and thicker than about $0.15\text{ }\mu\text{m}$ ([NIOSH, 2009](#)). Several studies, however, report the presence of very short fibres in lung and pleural tissue from patients with malignant mesothelioma ([Dodson et al., 2003](#); [Dodson et al., 2005](#); [Suzuki et al., 2005](#); [Dodson et al., 2007](#)), suggesting caution to exclude short fibres ($< 5\text{ }\mu\text{m}$) in the development of asbestos-related diseases ([Dodson et al., 2003](#)).

(c) Surface reactivity

In the last few decades, it has been accepted that, in addition to fibrous habit, surface reactivity also plays a role in the pathogenic effects of amphibole and chrysotile asbestos. The potential to release free radicals, among various other features, is considered the major determinant of the pathogenic response.

(i) Free-radical generation

Three different mechanisms of free-radical generation may take place at the surface of asbestos fibres, each one triggered by a different kind of active surface site: i) Fenton chemistry (yielding with H_2O_2 the generation of highly reactive hydroxyl radicals $\text{HO}\bullet$); ii) Haber-Weiss cycle (in the absence of H_2O_2 and Fe(II) , endogenous reductants allow progressive reduction of atmospheric oxygen to $\text{HO}\bullet$); iii) homolytic

rupture of a carbon-hydrogen bond in biomolecules, with generation of carbon-centred radicals in the target molecule (peptides, proteins, etc.) ([Hardy & Aust, 1995](#); [Fubini & Otero Areán, 1999](#); [Kamp & Weitzman, 1999](#)).

Mechanism i) is relevant only in cellular compartments where H_2O_2 is present (i.e. phagolysosomal environment in macrophages), while Mechanisms ii) and iii) may occur ubiquitously once fibres are inhaled. All mechanisms require the presence of iron ions. One stoichiometric chrysotile prepared by chemical synthesis, thus fully iron-free, was not active in free-radical generation (cell-free tests), did not induce lipid peroxidation, nor inhibit the pentose phosphate pathway in human lung epithelial cells, which is the opposite to what is found in natural specimens ([Gazzano et al., 2005](#)). When loaded with less than 1 wt.% of Fe^{3+} the synthetic chrysotile also became active ([Gazzano et al., 2007](#)). Asbestos fibres deprived of iron (following treatments with chelators) do not generate hydroxyl radicals ([Fubini et al., 1995](#)) or damage DNA, and are less potent in causing lipid peroxidation *in vitro* ([Hardy & Aust, 1995](#)). However, not all iron ions are equally reactive in free-radical generation, depending upon their coordination and oxidation state ([Shukla et al., 2003](#); [Bernstein et al., 2005](#)). $Fe(II)$ is active even in trace amounts ([Fubini et al., 1995](#)). Furthermore, Mechanism 3 requires isolated and poorly coordinated iron ions ([Martra et al., 2003](#); [Turci et al., 2007](#)). The surface sites involved in this reaction are oxidized and become inactive following thermal treatments: amphibole asbestos fibres heated up to 400°C in air ([Tomatis et al., 2002](#)) lose their potential in generating carboxyl radicals, but retain the reactivity for hydroxyl radicals, most likely through Mechanism 2, as long as their crystal structure is preserved. Conversely, the reduction of ferric into ferrous ions increases the radical activity ([Gulumian et al., 1993a](#)). The radical yield appears unrelated to the total amount of iron ([Gulumian et al., 1993b](#)), because

chrysotile shows a similar behaviour to crocidolite in cell-free tests despite the lower content of iron (3–6% versus 27%). Iron oxides (magnetite, haematite) are unable to produce radical species, whereas model solids, e.g. zeolites enriched with small amount of iron but with ions poorly coordinated and mostly in low valence state, are very reactive, particularly in hydrogen abstraction ([Fubini et al., 1995](#)).

Iron-derived free radicals are believed to produce a variety of cell effects including lipid peroxidation ([Ghio et al., 1998](#); [Gulumian, 1999](#)), DNA oxidation ([Aust & Eveleigh, 1999](#)), TNF-release and cell apoptosis ([Upadhyay & Kamp, 2003](#)), adhesion ([Churg et al., 1998](#)), and an increase of fibre uptake by epithelial cells ([Hobson et al., 1990](#)).

(ii) Iron bioavailability and biodeposition

Iron can be removed from asbestos fibres by intracellular chelators. If iron is mobilized from low-molecular-weight chelators, e.g. citrate, redox activity may be altered. The chelator-iron complex can diffuse throughout the cell, and catalyse the formation of hydroxyl radicals. Mobilization of iron was shown to correlate with DNA strand breaks and with DNA oxidation induced by crocidolite, amosite, and chrysotile ([Hardy & Aust, 1995](#)). In human lung epithelial and pleural mesothelial cells, the extent of iron mobilization was also related to the inactivation of epidermal growth factor receptor (EGFR/Erbb1), a step in the pathway leading to apoptosis ([Baldys & Aust, 2005](#)).

Mineral fibres may also acquire iron which, under certain conditions, may modify their reactivity. Erionite ([Dogan et al., 2008](#)) is able to bind both ferrous (through ion exchange) and ferric ions (through a precipitation or crystallization process). After ferrous-binding, erionite acquires the ability to generate hydroxyl radicals, and to catalyse DNA damage (DNA single-strand breaks); and after ferric-binding, the reactivity is acquired only in the presence of a reductant

(Hardy & Aust, 1995; Fach *et al.*, 2003; Ruda & Dutta, 2005). During their residence in the lung, asbestos fibres, like erionite fibres, acquire iron via a complex mechanism that may originate from the adsorption and disruption of ferritin, eventually yielding ferruginous bodies. These so-called asbestos bodies are preferentially formed onto long amphibole fibres but have also been found onto chrysotile fibres (Roggli, 2004). Although the presence of asbestos bodies in asbestos-related diseases is well documented, their biological role is still controversial. Iron deposition was thought to protect cells (Ghio *et al.*, 1997), but, deposited iron may become redox-active, thus enhancing the catalytic potential of the fibres (Ghio *et al.*, 2004). Asbestos bodies with amosite cores caused DNA single-strand breaks (Lund *et al.*, 1994); and increased radical damage to DNA was reported for ferritin-covered amosite in the presence of ascorbic acid (Otero-Areán *et al.*, 1999). Asbestos fibres might also disrupt normal iron homeostasis in the host by mobilizing and accumulating this metal (Ghio *et al.*, 2008).

Binding Fe (II) from solution increases iron mobilization from crocidolite by chelators, and induces DNA single-strand breaks. Increased lipid peroxidation and release of leukotriene B₄ is found in alveolar macrophages from rats treated with Fe (III)-loaded crocidolite, and Fe (III)-loaded crocidolite fibres induce more DNA single-strand breaks *in vitro* than do untreated crocidolite fibres (Ghio *et al.*, 1992).

It was suggested that crocidolite stimulates inducible nitric oxide synthase by decreasing iron bioavailability (Aldieri *et al.*, 2001).

(d) *Biopersistence, biodurability, and ecopersistence*

The residence time in the lung depends upon both the clearance mechanisms and physico-chemical processes taking place. Clearance mechanisms are mainly related to the shape and size of the particle, whereas chemical composition,

surface area, and structural parameters mainly affect leaching, dissolution, and breakage.

Selective leaching is more pronounced for serpentine asbestos than for amphiboles, which have no leachable “weak points” in their structure. Selective leaching of chrysotile occurs under strong acidic or chelating conditions, resulting in removal of Mg²⁺ ions. The kinetics vary according to the origin of the material, mechanical treatments, and associated contaminants, e.g. presence of nemalite (fibrous brucite) (Morgan, 1997). Chrysotile may lose magnesium *in vivo*, following phagocytosis by alveolar macrophages. The biological potential of magnesium-depleted chrysotile is greatly decreased (Langer & Nolan, 1994; Gulumian, 2005). Furthermore, leached fibres undergo breakage into shorter fibres, which may be cleared more readily from the lung. This accounts for the relatively low biopersistence of chrysotile compared to the amphiboles. The lungs of some chrysotile workers at autopsy contain low levels of chrysotile but substantial numbers of tremolite fibres, which is present in some chrysotile-bearing ores. For this reason, tremolite has been suggested to contribute to the carcinogenic effects seen in chrysotile miners (McDonald *et al.*, 1997; McDonald & McDonald, 1997; McDonald, 1998). Other asbestiform minerals may be associated with chrysotile, and, in some cases, modulate its toxicity, depending upon their amount and physicochemical characteristics. Balangeroite, occasionally intergrows with chrysotile (up to 5%) in the Balangero mine (Italy) and its surroundings. Balangeroite fibres have a different structure from amphiboles, and are poorly eco- and bio-durable (Favero-Longo *et al.*, 2009; Turci *et al.*, 2009). Balangeroite may contribute to the overall toxicity of chrysotile, but it cannot be compared to tremolite nor considered to be solely responsible for the excess of mesothelioma found in Balangero (Mirabelli *et al.*, 2008).

In the natural environment, weathering processes carried out by micro-organisms

may induce chrysotile-leaching, contributing to its bioattenuation ([Favero-Longo et al., 2005](#)). However, the dissolution of chrysotile is very low, because any breakdown of the silica framework takes place at a slow rate ([Hume & Rimstidt, 1992](#)), and is limited to a few layers in mild conditions ([Gronow, 1987](#)). Even in a strong acidic environment, the final product still retains a fibrous aspect at the nanoscale which is devoid of cations ([Wypych et al., 2005](#)).

4.3.2 Direct genotoxicity

Mineral fibres may directly induce genotoxicity by catalysing the generation of reactive oxygen species resulting in oxidized DNA bases and DNA strand breaks that can produce gene mutations if not adequately repaired ([IOM, 2006](#)). Both asbestos and erionite fibres can induce DNA damage mediated by reactive oxygen species. Asbestos fibres have also been shown to physically interfere with the mitotic apparatus, which may result in aneuploidy or polyploidy, and specific chromosomal alterations characteristic of asbestos-related cancer ([Jaurand, 1996](#)).

In addition to direct clastogenic and aneuploidogenic activities that may be induced following the translocation of asbestos fibres to target cell populations in the lungs, persistent inflammation and macrophage activation can secondarily generate additional reactive oxygen species, and reactive nitrogen species that can indirectly induce genotoxicity in addition to activation of intracellular signalling pathways, stimulation of cell proliferation and survival, and induction of epigenetic alterations (Fig. 4.2).

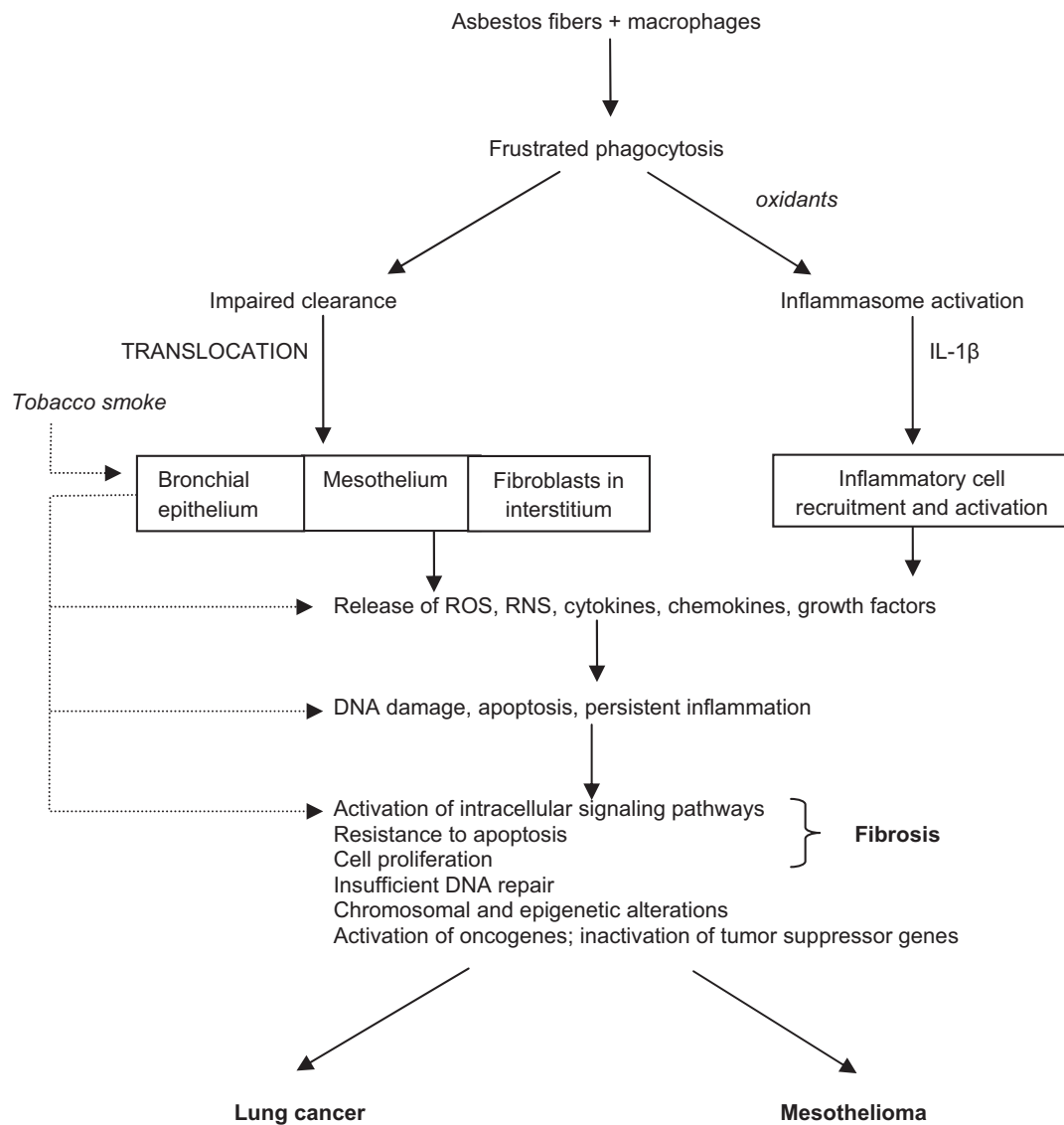
4.3.3 Indirect mechanisms

Asbestos fibres have unique and potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (asbestosis), and lung cancer ([Shukla et al., 2003](#)). Macrophages

express a variety of cell-surface receptors that bind to mineral fibres leading to phagocytosis, macrophage apoptosis, or macrophage activation. Receptors expressed by macrophages and other target cells in the lung that bind mineral fibres include MARCO, a scavenger receptor class A, and integrin receptors ([Boylan et al., 1995](#); [Gordon et al., 2002](#); [Arredouani et al., 2005](#)). Macrophage apoptosis has also been postulated to contribute to an increased incidence of autoimmune diseases in residents in Libby, Montana, USA, who are exposed to vermiculite contaminated with amphibole asbestos fibres ([Noonan et al., 2006](#); [Blake et al., 2008](#)).

Phagocytosis of asbestos fibres leads to the excess generation of reactive oxygen and nitrogen species by both direct (described in Sections 4.3.1 and 4.3.2), and indirect mechanisms ([Manning et al., 2002](#)). Alveolar macrophages phagocytize particulate materials and micro-organisms leading to assembly of NADPH oxidase in the phagolysosomal membrane that generates reactive oxygen species, which are potent antimicrobial agents. Asbestos fibres have elevated surface reactivity and redox-active iron that can generate hydroxyl radicals leading to lipid peroxidation, protein oxidation, and DNA damage resulting in lung injury that is amplified by persistent inflammation (Fig. 4.1 and 4.2). Recent investigations in genetically engineered mice have provided evidence for a key role of the NALP3 inflammasome as an intracellular sensor of the initial interactions between asbestos fibres and other crystals such as monosodium urate with macrophages ([Yu & Finlay, 2008](#)). The NALP3 inflammasome activates caspase-1 that cleaves IL-1 β precursor to active IL-1 β that is rapidly secreted ([Cassel et al., 2008](#); [Dostert et al., 2008](#)). This cytokine then triggers the recruitment and activation of additional inflammatory cells and the release of additional cytokines including TNF- α , IL-6, and IL-8 that perpetuate a prolonged inflammatory response to these biopersistent mineral dusts ([Shukla et al., 2003](#)).

Fig. 4.2 Proposed mechanism for the carcinogenicity of asbestos fibres



IL-1 β , interleukin -1 β ; RNS, reactive nitrogen species; ROS, reactive oxygen species.
Adapted from [Shukla et al. \(2003\)](#), [Kane \(2006\)](#), [Nymark et al. \(2008\)](#)

The generation of reactive oxygen species by asbestos fibres has also been associated with inducing apoptosis in mesothelial cells ([Broaddus et al., 1996](#)), and alveolar epithelial cells ([Aljandali et al., 2001](#)).

Asbestos fibres have been shown to contribute to the transformation of a variety of target cells from different species *in vitro*, and to induce lung tumours and malignant pleural mesothelioma in rodents following chronic inhalation ([Bernstein et al., 2005](#)). There are important species differences in the induction of asbestos-related cancers: rats are more susceptible to the induction of lung cancer, and hamsters are resistant to the induction of lung cancer but more susceptible to the development of malignant pleural mesothelioma ([IARC, 2002](#)). Subchronic inhalation studies using refractory ceramic fibres (RCF-1) suggest that the increased susceptibility of hamsters to developing malignant pleural mesothelioma may be related to greater translocation and accumulation of fibres in the pleural space, and an increased mesothelial cell proliferation in hamsters compared to rats ([Gelzleichter et al., 1999](#)). There are serious limitations in extrapolating these species differences to humans. First, most human lung cancers, even in asbestos-exposed individuals, are confounded by tobacco smoke that has potent independent genotoxic effects as reviewed later in Section 4.4.1. Second, diffuse malignant mesothelioma in humans is usually diagnosed at an advanced stage, and there are no reliable premalignant changes or biomarkers that may provide clues about the molecular pathogenesis of mesothelioma associated with exposure to asbestos or erionite fibres ([NIOSH, 2009](#)).

A unifying mechanism based on the experimental in-vitro cellular and in-vivo rodent models is proposed in Fig. 4.2.

Recent biochemical studies have confirmed that oxidative damage to cytosine is a plausible biological mechanism leading to epigenetic alterations and development of cancer in association

with persistent inflammation ([Valinluck & Sowers, 2007](#)). Neutrophils and macrophages are the source of reactive oxygen and nitrogen species triggered by phagocytosis of crystalline silica (quartz) or asbestos fibres. In addition, myeloperoxidase catalyses the formation of hypochlorous acid (HOCl) in neutrophils, and a specific peroxidase catalyses the formation of hypobromous acid (HOBr) in eosinophils ([Babior, 2000](#)). The formation of 8-oxoguanine, 5-hydroxymethylcytosine, or 5-hydroxycytosine interferes with DNA methylation and binding of methyl-CpG binding domains (MBDs). In contrast, chlorination or bromination of cytosine mimics 5-methylcytosine and induces heritable DNA methylation at previously unmethylated sites. Halogenated cytosines are also recognized by MBDs to facilitate chromatin remodelling. However, these modified bases are not recognized by DNA glycosylase, and are not repaired ([Valinluck & Sowers, 2007](#)).

This hypothesis linking heritable alterations in patterns of cytosine methylation with endogenous sources of oxidants released from inflammatory cells is a plausible explanation for the development of lung cancer and diffuse malignant mesothelioma associated with exposure to mineral fibres. Elevated neutrophils and eosinophils have been found in the pleural space following the inhalation of refractory ceramic fibres by hamsters and rats ([Gelzleichter et al., 1999](#)). Furthermore, myeloperoxidase activity has been detected in rodent lungs following exposure to asbestos fibres, whereas a decreased lung inflammation was observed in asbestos-exposed myeloperoxidase-null mice ([Haegens et al., 2005](#)). This indirect mechanism secondary to persistent inflammation may be responsible for altered epigenetic methylation profiles, which are characteristic of human malignant pleural mesotheliomas ([Christensen et al., 2009](#)).

4.4 Susceptible populations

Both exogenous environmental and occupational exposures and endogenous factors including genetic susceptibility contribute to the development of lung cancer ([NIOSH, 2009](#)) and diffuse malignant mesothelioma ([Weiner & Neragi-Miandoab, 2009](#)). The best example of an exogenous exposure that is a major cofactor with asbestos fibres in the development of cancer of the larynx and of the lung is tobacco smoking ([Table 4.3](#); [Table 4.4](#); [IARC, 2004](#); [IOM, 2006](#)). Additional environmental and occupational exposures are also risk factors for cancer of the larynx ([Table 4.3](#)) and of the lung ([Table 4.4](#)); these exposures are potential confounders in human epidemiological studies ([IOM, 2006](#)). Specific examples of these cofactors and other environmental and occupational exposures will be described in relationship to mechanisms of these cancers associated with mineral dust exposures.

4.4.1 Other risk factors for cancer of the lung and of the larynx, and diffuse malignant mesothelioma

(a) Tobacco smoke

Co-exposure to tobacco smoke and asbestos fibres is at least additive and possibly multiplicative in the development of lung cancer ([Vainio & Boffetta, 1994](#)). The inhalation of tobacco smoke ([Walser et al., 2008](#)) as well as mineral fibres is associated with excess generation of reactive oxygen and nitrogen metabolites, cell injury and apoptosis, and persistent lung inflammation ([Shukla et al., 2003](#); [IARC, 2004](#)). Excess oxidant generation has been shown to enhance the penetration of asbestos fibres into respiratory epithelial cells, and to impair fibre clearance ([McFadden et al., 1986](#); [Churg et al., 1989](#)), as well as altering the metabolism and detoxification of tobacco smoke carcinogens ([Nymark et al., 2008](#)). Asbestos fibres can also adsorb tobacco smoke

Table 4.3 Risk factors for the development of cancer of the larynx

Exposure	Reference
Active tobacco smoking	IARC (1986, 2004, 2012d)
Alcohol	IARC (1988, 2010, 2012d)
Mustard gas	IARC (1987a, 2012e)
Inorganic acid mists containing sulfuric acid	IARC (1992, 2012e)
Asbestos fibres	IOM (2006), IARC (2012b)
Human papilloma virus (HPV): types 6, 11, 16, 18	IARC (2007, 2012c)
limited evidence	

Compiled by the Working Group

carcinogens and metals and facilitate their transport into the lungs ([IOM, 2006](#)). Asbestos fibres have also been shown to activate growth-factor receptors and cell-signalling pathways that stimulate cell proliferation and promote cell survival ([Albrecht et al., 2004](#)). In summary, co-exposures to tobacco smoke and mineral fibres can amplify acquired genetic mutations induced by tobacco smoke carcinogens, and amplify cell proliferation in response to tissue injury leading to an increased risk for the development of cancer of the larynx and of the lung ([Nymark et al., 2008](#)).

(b) Other occupational and environmental exposures

Alcohol and occupational exposure to irritants ([Table 4.3](#)) also contribute to the development of cancer of the larynx. These irritants, similar to inhalation of tobacco smoke, can cause repeated episodes of injury to the respiratory epithelium, resulting in metaplasia and dysplasia ([Olshan, 2006](#)); these preneoplastic lesions may then acquire additional molecular alterations and progress towards the development of invasive lung or laryngeal carcinoma. Other occupational exposures responsible for the development of lung cancer include direct-acting carcinogens such as ionizing radiation ([IARC, 2000, 2012a](#)), and metals (reviewed in [IARC, 2012b](#)).

IARC MONOGRAPHS – 100C

Table 4.4 Risk factors for the development of cancer of the lung

Exposure	Reference
Active and passive tobacco smoking	IARC (2004, 2012d)
Ionizing radiation	IARC (2000, 2012a)
Respirable dusts and fibres:	
Asbestos	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Crystalline silica (quartz)	IARC (1997, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987) , McDonald et al. (2004) , IARC (2012b)
Bis(chloromethyl)ether and chloromethyl methyl ether	IARC (1987a, 2012e)
Arsenic and arsenic compounds	IARC (1987a, 2012b)
Beryllium	IARC (1993, 2012b)
Cadmium and cadmium compounds	IARC (1993, 2012b)
Hexavalent chromium	IARC (1990, 2012b)
Nickel sulfate, oxides, and sulfides	IARC (1990, 2012b)
Soots	IARC (1985, 1987a, 2012e)

Compiled by the Working Group

The strongest risk factors associated with the development of diffuse malignant mesothelioma include environmental or occupational exposures to erionite, asbestos fibres, and talc or vermiculite contaminated with asbestos fibres ([Table 4.5](#); [NIOSH, 2009](#)). It is unknown whether the carcinogenic effects of exposure to mixed dusts contaminated with asbestos fibres can be entirely attributed to the asbestos fibres or whether co-exposure to talc or vermiculite dusts potentiates the retention and/or biological activity of asbestos fibres *in vivo* ([Davis, 1996](#)). The occurrence of talc pneumoconiosis and its relationship to other mineral dust contaminants including quartz and tremolite was recently reviewed ([IARC, 2010](#)). In-vitro assays of talc cytotoxicity were also summarized ([IARC, 2010](#)). No experimental studies have been published assessing the cytotoxicity of vermiculite contaminated with asbestos fibres. A sample of the mixture of amphibole fibres associated with Libby vermiculite ore has been shown to induce cytotoxicity and oxidative stress in macrophages *in vitro* ([Blake et al., 2007](#)).

(c) *SV40 and HPV viruses*

Two human DNA tumour viruses have been linked with an increased risk for cancer of the larynx ([Table 4.3](#); high-risk subtypes of human papillomavirus (HPV)) and diffuse malignant mesothelioma ([Table 4.5](#); Simian virus 40 (SV40)).

The evidence for HPV 16 in the development of cancer of the larynx has been evaluated as limited, although it has been implicated as an independent risk factor in the development of other squamous cell carcinomas arising in the head and neck region ([IARC, 2007, 2012c](#)).

The association between exposure to SV40 and asbestos fibres in the development of diffuse malignant mesothelioma is highly controversial ([Butel & Lednický, 1999](#); [Gazdar et al., 2002](#); [Shah, 2004](#); [IOM, 2006](#)). SV40 is not an essential cofactor for the development of mesothelioma; for example, residents of the Cappadocian villages in Turkey have a very high risk for diffuse malignant mesothelioma but do not have evidence of SV40 exposure ([Dogan et al., 2006](#)). Although there are several in-vitro mechanistic

Table 4.5 Risk factors for the development of diffuse malignant mesothelioma

Exposure	Reference
Asbestos fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987) , IARC (1987a, 2012e) , McDonald et al. (2004)
Thorotrast	IARC (2001, 2012a)

Compiled by the Working Group

studies that support a role for SV40 viral oncogenes in the transformation of mesothelial cells, the human epidemiological evidence is inconclusive to support a causal association ([Weiner & Neragi-Miandoab, 2009](#)).

4.4.2 Genetic susceptibility

(a) Cancer of the lung

Tobacco smoke is the major cause of cancer of the lung; however, only a few rare hereditary syndromes are associated with an increased risk of lung, as well as other cancers: Bloom syndrome, Li-Fraumeni syndrome, and hereditary retinoblastoma ([Lindor et al., 2006](#)). Other genetic polymorphisms in genes related to the metabolism and detoxification of tobacco smoke carcinogens, antioxidant defenses, and DNA repair have been suggested as predisposing factors for the development of lung cancer, although individually they contribute minimally to an increased risk ([IOM, 2006](#)). Attempts have been made to identify genetic polymorphisms in enzymes involved in xenobiotic metabolism and antioxidant defense that increase the risk for asbestos-related lung cancer; however, no consistent associations have been found ([Nymark et al., 2008](#)).

(b) Diffuse malignant mesothelioma

With the exception of certain populations who have been exposed environmentally to asbestos or erionite fibres since birth ([NIOSH, 2009](#)), the development of diffuse malignant mesothelioma even in occupationally exposed workers is less common than the development of lung cancer ([Nymark et al., 2008](#)). This observation has led to the hypothesis that there may be a genetic predisposition to the development of diffuse malignant mesothelioma following exposure to asbestos or erionite fibres. Isolated case reports provide examples of diffuse malignant mesothelioma in patients with neurofibromatosis type 2 ([Baser et al., 2002](#)) or Li-Fraumeni syndrome ([Heineman et al., 1996](#)) who are also exposed to asbestos. Several reports of familial cases of diffuse malignant mesothelioma are complicated by a common household exposure history ([Weiner & Neragi-Miandoab, 2009](#)). The strongest association between environmental exposure to erionite and genetic susceptibility to diffuse malignant mesothelioma has been provided by pedigree analysis of residents in the Cappadocia region of Turkey ([Dogan et al., 2006](#)). However, there is skepticism about the accuracy of this analysis, and a recent review indicated that familial clusters can account for only 1.4% of cases of mesothelioma in Italy between 1978–2005 ([Ascoli et al., 2007](#); [Ugolini et al., 2008](#)). One study has reported an association between genetic polymorphisms in the X-ray complementing group 1 gene (XRCC1) and the development of malignant mesothelioma in a population exposed to asbestos fibres ([Dianzani et al., 2006](#)). More sensitive genome-wide association studies may uncover new markers for genetic susceptibility that predict increase risks of developing diffuse malignant mesothelioma following exposure to asbestos or erionite fibres.

4.5 Synthesis

The mechanistic basis for asbestos carcinogenicity is a complex interaction between crystalline mineral fibres and target cells *in vivo*. The most important physicochemical properties of asbestos fibres related to pathogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Multiple direct and indirect mechanisms have been proposed based on numerous in-vitro cellular assays, and acute and subchronic animal bioassays. These complex mechanisms most likely interact at multiple stages during the development of lung cancer and diffuse malignant mesothelioma.

The following general mechanisms have been proposed for the carcinogenicity of asbestos fibres (Fig. 4.1; Fig. 4.2):

1. Direct interaction between asbestos fibres and target cells *in vitro*:

- Asbestos and erionite fibres have been shown to generate free radicals that directly induce genotoxicity as assessed by DNA breaks and oxidized bases in DNA.
- Asbestos fibres have also been shown to interfere with the mitotic apparatus by direct physical interaction resulting in aneuploidy and polyploidy.

2. Indirect mechanisms:

- In laboratory animals, asbestos fibres have been shown to induce macrophage activation and persistent inflammation that generate reactive oxygen and nitrogen species contributing to tissue injury, genotoxicity, and epigenetic alterations. Persistent inflammation and chronic oxidative stress have been associated with the activation of intracellular signalling pathways, resistance to apoptosis, and stimulation of cell proliferation.

There are significant species differences in the responses of the respiratory tract to the inhalation of asbestos fibres. The biological

mechanisms responsible for these species differences are unknown. Based on comparative animal experimental studies, there may be differences in deposition and clearance of fibres in the lungs, in severity of fibrosis, in kinetics of translocation of fibres to the pleura, and in levels or types of antioxidant defense mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite). Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary. Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. For cancer of the colorectum, the Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*.

There is *sufficient evidence* in experimental animals for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite).

All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) are *carcinogenic to humans* (Group 1).

References

- ACGIH (2007). Documentation of the TLVs and BEIs with Other Worldwide Occupational Exposure Values - 2007, Cincinnati, OH [CD-ROM]
- Acheson ED, Gardner MJ, Pippard EC, Grime LP (1982). Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med*, 39: 344–348. PMID:6291580
- Addison J & Davies LS (1990). Analysis of amphibole asbestos in chrysotile and other minerals. *Ann Occup Hyg*, 34: 159–175. doi:10.1093/annhyg/34.2.159 PMID:2169219

- Albin M, Jakobsson K, Attewell R *et al.* (1990). Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *Br J Ind Med*, 47: 602–610. PMID:2207031
- Albin M, Magnani C, Krstev S *et al.* (1999). Asbestos and cancer: An overview of current trends in Europe. *Environ Health Perspect*, 107: Suppl 2289–298. PMID:10350513
- Albrecht C, Borm PJ, Unfried K (2004). Signal transduction pathways relevant for neoplastic effects of fibrous and non-fibrous particles. *Mutat Res*, 553: 23–35. PMID:15288530
- Aldieri E, Ghigo D, Tomatis M *et al.* (2001). Iron inhibits the nitric oxide synthesis elicited by asbestos in murine macrophages. *Free Radic Biol Med*, 31: 412–417. doi:10.1016/S0891-5849(01)00612-8 PMID:11461780
- Aliyu OA, Cullen MR, Barnett MJ *et al.* (2005). Evidence for excess cancer of the colorectum incidence among asbestos-exposed men in the Beta-Carotene and Retinol Efficacy Trial. *Am J Epidemiol*, 162: 868–878. doi:10.1093/aje/kwi285 PMID:16177148
- Aljandali A, Pollack H, Yeldandi A *et al.* (2001). Asbestos causes apoptosis in alveolar epithelial cells: role of iron-induced free radicals. *J Lab Clin Med*, 137: 330–339. doi:10.1067/mlc.2001.114826 PMID:11329530
- Altomare DA, Vaslet CA, Skele KL *et al.* (2005). A mouse model recapitulating molecular features of human mesothelioma. *Cancer Res*, 65: 8090–8095. doi:10.1158/0008-5472.CAN-05-2312 PMID:16166281
- Amandus HE & Wheeler R (1987). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. *Am J Ind Med*, 11: 15–26. doi:10.1002/ajim.4700110103 PMID:3028136
- Amandus HE, Wheeler R, Jankovic J, Tucker J (1987). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part I. Exposure estimates. *Am J Ind Med*, 11: 1–14. doi:10.1002/ajim.4700110102 PMID:3028135
- Anderson HA, Lilis R, Daum SM *et al.* (1976). Household-contact asbestos neoplastic risk. *Ann N Y Acad Sci*, 271: 1 Neoplasia in 311–323. doi:10.1111/j.1749-6632.1976.tb23127.x PMID:1069520
- Apostolou S, Balsara BR, Testa JR *et al.* (2006). *Cytogenetics of malignant mesothelioma*. In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies*. New York: Springer Science & Business Media, Inc., pp. 101–111.
- Arredouani MS, Palecanda A, Koziel H *et al.* (2005). MARCO is the major binding receptor for unopsonized particles and bacteria on human alveolar macrophages. *J Immunol*, 175: 6058–6064. PMID:16237101
- Ascoli V, Cavone D, Merler E *et al.* (2007). Mesothelioma in blood related subjects: report of 11 clusters among 1954 Italy cases and review of the literature. *Am J Ind Med*, 50: 357–369. doi:10.1002/ajim.20451 PMID:17407142
- ATSDR (2001). Toxicological Profile for Asbestos (TP-61). US Dept. of Health & Human Services.
- Aust AE & Eveleigh JF (1999). Mechanisms of DNA oxidation. *Proc Soc Exp Biol Med*, 222: 246–252. doi:10.1046/j.1525-1373.1999.d01-141.x PMID:10601883
- Babior BM (2000). Phagocytes and oxidative stress. *Am J Med*, 109: 33–44. doi:10.1016/S0002-9343(00)00481-2 PMID:10936476
- Baldys A & Aust AE (2005). Role of iron in inactivation of epidermal growth factor receptor after asbestos treatment of human lung and pleural target cells. *Am J Respir Cell Mol Biol*, 32: 436–442. doi:10.1165/rcmb.2004-0133OC PMID:15626777
- Baris I, Simonato L, Artvinli M *et al.* (1987). Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. *Int J Cancer*, 39: 10–17. doi:10.1002/ijc.2910390104 PMID:3025107
- Baris YI & Grandjean P (2006). Prospective study of mesothelioma mortality in Turkish villages with exposure to fibrous zeolite. *J Natl Cancer Inst*, 98: 414–417. doi:10.1093/jnci/djj106 PMID:16537834
- Baser ME, De Rienzo A, Altomare D *et al.* (2002). Neurofibromatosis 2 and malignant mesothelioma. *Neurology*, 59: 290–291. PMID:12136076
- Bégin R, Gauthier JJ, Desmeules M, Ostiguy G (1992). Work-related mesothelioma in Québec, 1967–1990. *Am J Ind Med*, 22: 531–542. doi:10.1002/ajim.4700220408 PMID:1332466
- Berman DW & Crump KS (2008a). A meta-analysis of asbestos-related cancer risk that addresses fibre size and mineral type. *Crit Rev Toxicol*, 38: Suppl 149–73. doi:10.1080/10408440802273156 PMID:18686078
- Berman DW & Crump KS (2008b). Update of potency factors for asbestos-related lung cancer and mesothelioma. *Crit Rev Toxicol*, 38: Suppl 11–47. doi:10.1080/10408440802276167 PMID:18671157
- Bernstein D, Castranova V, Donaldson K *et al.* (2005). Testing of fibrous particles: short-term assays and strategies. *Inhal Toxicol*, 17: 497–537. PMID:16040559
- Berrino F, Richiardi L, Boffetta P *et al.* Milan JEM Working Group (2003). Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland. *Cancer Causes Control*, 14: 213–223. doi:10.1023/A:1023661206177 PMID:12814200
- Berry G (1999). Models for mesothelioma incidence following exposure to fibres in terms of timing and duration of exposure and the biopersistence of the fibres. *Inhal Toxicol*, 11: 111–130. doi:10.1080/089583799197203 PMID:10380162
- Berry G, Newhouse ML, Wagner JC (2000). Mortality from all cancers of asbestos factory workers in east London 1933–80. *Occup Environ Med*, 57: 782–785. doi:10.1136/oem.57.11.782 PMID:11024203

IARC MONOGRAPHS – 100C

- Bertolotti M, Ferrante D, Mirabelli D *et al.* (2008). Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy) *Epidemiol Prev*, 32: 218–228. PMID:19186504
- Blake DJ, Bolin CM, Cox DP *et al.* (2007). Internalization of Libby amphibole asbestos and induction of oxidative stress in murine macrophages. *Toxicol Sci*, 99: 277–288. doi:10.1093/toxsci/kfm166 PMID:17578862
- Blake DJ, Wetzel SA, Pfau JC (2008). Autoantibodies from mice exposed to Libby amphibole asbestos bind SSA/Ro52-enriched apoptotic blebs of murine macrophages. *Toxicology*, 246: 172–179. doi:10.1016/j.tox.2008.01.008 PMID:18295955
- Blount AM (1991). Amphibole content of cosmetic and pharmaceutical talcs. *Environ Health Perspect*, 94: 225–230. doi:10.2307/3431315 PMID:1659533
- Boutin C, Dumortier P, Rey F *et al.* (1996). Black spots concentrate oncogenic asbestos fibres in the parietal pleura. Thoracoscopic and mineralogic study. *Am J Respir Crit Care Med*, 153: 444–449. PMID:8542156
- Boylan AM, Sanan DA, Sheppard D, Broaddus VC (1995). Vitronectin enhances internalization of crocidolite asbestos by rabbit pleural mesothelial cells via the integrin alpha v beta 5. *J Clin Invest*, 96: 1987–2001. doi:10.1172/JCI118246 PMID:7560092
- Broaddus VC, Yang L, Scavo LM *et al.* (1996). Asbestos induces apoptosis of human and rabbit pleural mesothelial cells via reactive oxygen species. *J Clin Invest*, 98: 2050–2059. doi:10.1172/JCI119010 PMID:8903324
- Bruno C, Comba P, Zona A (2006). Adverse health effects of fluoro-edenitic fibers: epidemiological evidence and public health priorities. *Ann N Y Acad Sci*, 1076: 778–783. doi:10.1196/annals.1371.020 PMID:17119254
- Butel JS & Lednický JA (1999). Cell and molecular biology of simian virus 40: implications for human infections and disease. *J Natl Cancer Inst*, 91: 119–134. doi:10.1093/jnci/91.13.1166a PMID:9923853
- Cacciotti P, Mutti L, Gaudino G (2006). *Growth factors and malignant mesothelioma*. In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies*. Pass HI, Vogelzang NJ Carbone M, editors. New York: Springer Science & Business Media, Inc., pp. 112–123.
- Camus M, Siemiatycki J, Meek B (1998). Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *N Engl J Med*, 338: 1565–1571. doi:10.1056/NEJM199805283382201 PMID:9603793
- Cantor KP (1997). Drinking water and cancer. *Cancer Causes Control*, 8: 292–308. doi:10.1023/A:1018444902486 PMID:9498894
- Cassel SL, Eisenbarth SC, Iyer SS *et al.* (2008). The Nalp3 inflammasome is essential for the development of silicosis. *Proc Natl Acad Sci USA*, 105: 9035–9040. doi:10.1073/pnas.0803933105 PMID:18577586
- Catalano A, Strizzi L, Procopio A (2005). *Angiogenesis and mesothelioma*. In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies*. Pass HI, Vogelzang NJ, Carbone M, editors. New York: Springer Science & Business Media, Inc., pp. 141–150.
- Christensen BC, Godleski JJ, Marsit CJ *et al.* (2008). Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma. *Carcinogenesis*, 29: 1555–1559. doi:10.1093/carcin/bgn059 PMID:18310086
- Christensen BC, Houseman EA, Godleski JJ *et al.* (2009). Epigenetic profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome. *Cancer Res*, 69: 227–234. doi:10.1158/0008-5472.CAN-08-2586 PMID:19118007
- Churg A, Hobson J, Berean K, Wright J (1989). Scavengers of active oxygen species prevent cigarette smoke-induced asbestos fibre penetration in rat tracheal explants. *Am J Pathol*, 135: 599–603. PMID:2801882
- Churg A, Sun J, Zay K (1998). Cigarette smoke increases amosite asbestos fibre binding to the surface of tracheal epithelial cells. *Am J Physiol*, 275: L502–L508. PMID:9728044
- Churg A & Warnock ML (1980). Asbestos fibres in the general population. *Am Rev Respir Dis*, 122: 669–678. PMID:7447151
- Cocco P, Palli D, Buiatti E *et al.* (1994). Occupational exposures as risk factors for gastric cancer in Italy. *Cancer Causes Control*, 5: 241–248. doi:10.1007/BF01830243 PMID:8061172
- Coffin DL, Cook PM, Creason JP (1992). Relative mesothelioma induction in rats by mineral fibres: comparison with residual pulmonary mineral fibre number and epidemiology. *Inhal Toxicol*, 4: 273–300. doi:10.3109/08958379209145671
- Comba P, Gianfagna A, Paoletti L (2003). Pleural mesothelioma cases in Biancavilla are related to a new fluoro-edenite fibrous amphibole. *Arch Environ Health*, 58: 229–232. doi:10.3200/AEOH.58.4.229-232 PMID:14655903
- Conforti PM, Kanarek MS, Jackson LA *et al.* (1981). Asbestos in drinking water and cancer in the San Francisco Bay Area: 1969–1974 incidence. *J Chronic Dis*, 34: 211–224. doi:10.1016/0021-9681(81)90065-5 PMID:7240361
- Cullen MR (1996). The amphibole hypothesis of asbestos-related cancer—gone but not forgotten. *Am J Public Health*, 86: 158–159. doi:10.2105/AJPH.86.2.158 PMID:8633728
- Cullen MR & Baloyi RS (1991). Chrysotile asbestos and health in Zimbabwe: I. Analysis of miners and millers compensated for asbestos-related diseases since independence (1980). *Am J Ind Med*, 19: 161–169. doi:10.1002/ajim.4700190204 PMID:1847001
- Cullen RT, Searl A, Buchanan D *et al.* R. T. Cullen, A. Searl, D. Buchanan (2000). Pathogenicity of a special-purpose glass microfibre (E glass) relative to

- another glass microfibre and amosite asbestos. *Inhal Toxicol*, 12: 959–977. doi:10.1080/08958370050138012 PMID:10989371
- Davis JM (1996). Mixed fibrous and non-fibrous dusts exposures and interactions between agents in fibre carcinogenesis. *IARC Sci Pub*, 140:127
- Davis JM, Addison J, Bolton RE *et al.* (1985). Inhalation studies on the effects of tremolite and brucite dust in rats. *Carcinogenesis*, 6: 667–674. doi:10.1093/carcin/6.5.667 PMID:2988806
- Davis JM, Addison J, Bolton RE *et al.* (1986a). Inhalation and injection studies in rats using dust samples from chrysotile asbestos prepared by a wet dispersion process. *Br J Exp Pathol*, 67: 113–129. PMID:3004552
- Davis JM, Addison J, Bolton RE *et al.* (1986b). The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. *Br J Exp Pathol*, 67: 415–430. PMID:2872911
- Davis JM, Beckett ST, Bolton RE *et al.* (1978). Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. *Br J Cancer*, 37: 673–688. PMID:656299
- Davis JM, Beckett ST, Bolton RE, Donaldson K (1980a). The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. *Br J Exp Pathol*, 61: 272–280. PMID:7426382
- Davis JM, Beckett ST, Bolton RE, Donaldson K (1980b). A comparison of the pathological effects in rats of the UICC reference samples of amosite and chrysotile with those of amosite and chrysotile collected from the factory environment. *IARC Sci Publ*, 30: 285–292. PMID:7239647
- Davis JM, Bolton RE, Douglas AN *et al.* (1988). Effects of electrostatic charge on the pathogenicity of chrysotile asbestos. *Br J Ind Med*, 45: 292–299. PMID:2837270
- Davis JM, Bolton RE, Miller BG, Niven K (1991b). Mesothelioma dose response following intraperitoneal injection of mineral fibres. *Int J Exp Pathol*, 72: 263–274. PMID:1843255
- Davis JM, Brown DM, Cullen RT *et al.* (1996). A comparison of methods of determining and predicting pathogenicity of mineral fibres. *Inhal Toxicol*, 8: 747–770. doi:10.3109/08958379608995209
- Davis JM & Jones AD (1988). Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. *Br J Exp Pathol*, 69: 717–737. PMID:2848570
- Davis JM, Jones AD, Miller BG (1991a). Experimental studies in rats on the effects of asbestos inhalation coupled with the inhalation of titanium dioxide or quartz. *Int J Exp Pathol*, 72: 501–525. PMID:1742204
- Dement JM & Brown DP (1994). Lung cancer mortality among asbestos textile workers: a review and update. *Ann Occup Hyg*, 38: 525–532, 412. doi:10.1093/annhyg/38.4.525 PMID:7978974
- Dement JM, Brown DP, Okun A (1994). Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. *Am J Ind Med*, 26: 431–447. doi:10.1002/ajim.4700260402 PMID:7810543
- Dement JM, Kuempel ED, Zumwalde RD *et al.* (2008). Development of a fibre size-specific job-exposure matrix for airborne asbestos fibres. *Occup Environ Med*, 65: 605–612. doi:10.1136/oem.2007.033712 PMID:17984198
- Demers RY, Burns PB, Swanson GM (1994). Construction occupations, asbestos exposure, and cancer of the colon and rectum. *J Occup Med*, 36: 1027–1031. PMID:7823215
- Dianzani I, Gibello L, Biava A *et al.* (2006). Polymorphisms in DNA repair genes as risk factors for asbestos-related malignant mesothelioma in a general population study. *Mutat Res*, 599: 124–134. PMID:16564556
- Dodson RF & Atkinson MA (2006). Measurements of asbestos burden in tissues. *Ann N Y Acad Sci*, 1076: 281–291. doi:10.1196/annals.1371.015 PMID:17119209
- Dodson RF, Atkinson MA, Levin JL (2003). Asbestos fibre length as related to potential pathogenicity: a critical review. *Am J Ind Med*, 44: 291–297. doi:10.1002/ajim.10263 PMID:12929149
- Dodson RF, Graef R, Shepherd S *et al.* (2005). Asbestos burden in cases of mesothelioma from individuals from various regions of the United States. *Ultrastruct Pathol*, 29: 415–433. doi:10.1080/019131290945682 PMID:16257868
- Dodson RF, Shepherd S, Levin J, Hammar SP (2007). Characteristics of asbestos concentration in lung as compared to asbestos concentration in various levels of lymph nodes that collect drainage from the lung. *Ultrastruct Pathol*, 31: 95–133. doi:10.1080/01913120701423907 PMID:17613992
- Dodson RF, Williams MG Jr, Corn CJ *et al.* (1990). Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers. *Am Rev Respir Dis*, 142: 843–847. PMID:2171386
- Dogan AU, Baris YI, Dogan M *et al.* (2006). Genetic predisposition to fibre carcinogenesis causes a mesothelioma epidemic in Turkey. *Cancer Res*, 66: 5063–5068. doi:10.1158/0008-5472.CAN-05-4642 PMID:16707428
- Dogan AU, Dogan M, Hoskins JA (2008). Erionite series minerals: mineralogical and carcinogenic properties. *Environ Geochem Health*, 30: 367–381. doi:10.1007/s10653-008-9165-x PMID:18347916
- Doll R (1955). Mortality from lung cancer in asbestos workers. *Br J Ind Med*, 12: 81–86. PMID:14363586
- Donaldson K & Golyasny N (1995). Cytogenetic and pathogenic effects of long and short amosite asbestos. *J Pathol*, 177: 303–307. doi:10.1002/path.1711770313 PMID:8551393
- Donaldson K, Li XY, Dogra S *et al.* (1992). Asbestos-stimulated tumour necrosis factor release from alveolar macrophages depends on fibre length and opsonization.

IARC MONOGRAPHS – 100C

- J Pathol*, 168: 243–248. doi:10.1002/path.1711680214 PMID:1334143
- Donaldson K & Tran CL (2004). An introduction to the short-term toxicology of respirable industrial fibres. *Mutat Res*, 553: 5–9. PMID:15288528
- Dostert C, Pétrilli V, Van Bruggen R *et al.* (2008). Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science*, 320: 674–677. doi:10.1126/science.1156995 PMID:18403674
- Dumortier P, Coplū L, Broucke I *et al.* (2001). Erionite bodies and fibres in bronchoalveolar lavage fluid (BALF) of residents from Tuzköy, Cappadocia, Turkey. *Occup Environ Med*, 58: 261–266. doi:10.1136/oem.58.4.261 PMID:11245743
- Dumortier P, De Vuyst P, Yernault JC (1989). Non-fibrous inorganic particles in human bronchoalveolar lavage fluids. *Scanning Microsc*, 3: 1207–1216, discussion 1217–1218. PMID:2561220
- Edelman DA (1988). Exposure to asbestos and the risk of gastrointestinal cancer: a reassessment. *Br J Ind Med*, 45: 75–82. PMID:3342198
- Enterline PE, Hartley J, Henderson V (1987). Asbestos and cancer: a cohort followed up to death. *Br J Ind Med*, 44: 396–401. PMID:3606968
- Esteller M (2005). Dormant hypermethylated tumour suppressor genes: questions and answers. *J Pathol*, 205: 172–180. doi:10.1002/path.1707 PMID:15643671
- EU (1999). Commission Directive 1999/77/EC of 26 July 1999. Official Journal of the European Communities. [L207/18 – L207/20]
- EU (2003). Directive 2003/18/EC of the European Parliament and of the Council of 27 March 2003 amending Council Directive 83/477/EEC on the protection of workers from the risks related to exposure to asbestos at work. Official Journal L 097, 15/04/2003 P. 0048 – 0052.
- Fach E, Kristovich R, Long JF *et al.* (2003). The effect of iron on the biological activities of erionite and mordenite. *Environ Int*, 29: 451–458. doi:10.1016/S0160-4120(02)00193-9 PMID:12705942
- Favero-Longo SE, Turci F, Tomatis M *et al.* (2005). Chrysotile asbestos is progressively converted into a non-fibrous amorphous material by the chelating action of lichen metabolites. *J Environ Monit*, 7: 764–766. doi:10.1039/b507569f PMID:16049575
- Favero-Longo SE, Turci F, Tomatis M *et al.* (2009). The effect of weathering on ecopersistence, reactivity, and potential toxicity of naturally occurring asbestos and asbestiform mineral. *J Toxicol Environ Health A*, 72: 305–314. PMID:19184746.
- Feron VJ, Scherrenberg PM, Immel HR, Spit BJ (1985). Pulmonary response of hamster to fibrous glass: chronic effects of repeated intratracheal instillation with or without benzo[a]pyrene. *Carcinogenesis*, 6: 1495–1499. doi:10.1093/carcin/6.10.1495 PMID:4042277
- Ferrante D, Bertolotti M, Todesco A *et al.* (2007). Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect*, 115: 1401–1405. PMID:17938727
- Finkelstein MM (1983). Mortality among long-term employees of an Ontario asbestos-cement factory. *Br J Ind Med*, 40: 138–144. PMID:6830709
- Fredriksson M, Bengtsson NO, Hardell L, Axelson O (1989). Colon cancer, physical activity, and occupational exposures. A case-control study. *Cancer*, 63: 1838–1842. doi:10.1002/1097-0142(19900501)63:9<1838::AID-CNCR2820630930>3.0.CO;2-4 PMID:2702592
- Frumkin H & Berlin J (1988). Asbestos exposure and gastrointestinal malignancy review and meta-analysis. *Am J Ind Med*, 14: 79–95. doi:10.1002/ajim.4700140110 PMID:3044065
- Fubini B (1997). Surface reactivity in the pathogenic response to particulates. *Environ Health Perspect*, 105: Suppl 51013–1020. doi:10.2307/3433502 PMID:9400693
- Fubini B & Fenoglio I (2007). Toxic potential of mineral dusts. *Elements*, 3: 407–414. doi:10.2113/GSELEMENTS.3.6.407
- Fubini B, Mollo L, Giamello E (1995). Free radical generation at the solid/liquid interface in iron containing minerals. *Free Radic Res*, 23: 593–614. doi:10.3109/10715769509065280 PMID:8574353
- Fubini B & Otero Areán C (1999). Chemical aspects of the toxicity of inhaled mineral dusts. *Chem Soc Rev*, 28: 373–381. doi:10.1039/a805639k
- Gamble J (2008). Risk of gastrointestinal cancers from inhalation and ingestion of asbestos. *Regul Toxicol Pharmacol*, 52: Suppl S124–S153. doi:10.1016/j.yrtph.2007.10.009 PMID:18078700
- Garabrant DH, Peters RK, Homa DM (1992). Asbestos and colon cancer: lack of association in a large case-control study. *Am J Epidemiol*, 135: 843–853. PMID:1585897
- Gardner MJ, Winter PD, Pannett B, Powell CA (1986). Follow up study of workers manufacturing chrysotile asbestos cement products. *Br J Ind Med*, 43: 726–732. PMID:3024695
- Gazdar AF, Butel JS, Carbone M (2002). SV40 and human tumours: myth, association or causality? *Nat Rev Cancer*, 2: 957–964. doi:10.1038/nrc947 PMID:12459734
- Gazzano E, Foresti E, Lesci IG *et al.* (2005). Different cellular responses evoked by natural and stoichiometric synthetic chrysotile asbestos. *Toxicol Appl Pharmacol*, 206: 356–364. doi:10.1016/j.taap.2004.11.021 PMID:16039947
- Gazzano E, Turci F, Foresti E *et al.* (2007). Iron-loaded synthetic chrysotile: a new model solid for studying the role of iron in asbestos toxicity. *Chem Res Toxicol*, 20: 380–387. doi:10.1021/tx600354f PMID:17315889
- Gelzleichter TR, Bermudez E, Mangum JB *et al.* (1999). Comparison of pulmonary and pleural responses of rats and hamsters to inhaled refractory ceramic fibres.

- Toxicol Sci*, 49: 93–101. doi:10.1093/toxsci/49.1.93 PMID:10367346
- Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM (1992). Occupational exposures and cancer of the colon and rectum. *Am J Ind Med*, 22: 291–303. doi:10.1002/ajim.4700220303 PMID:1519614
- Germani D, Belli S, Bruno C *et al.* (1999). Cohort mortality study of women compensated for asbestosis in Italy. *Am J Ind Med*, 36: 129–134. doi:10.1002/(SICI)1097-0274(199907)36:1<129::AID-AJIM18>3.0.CO;2-9 PMID:10361597
- Ghio AJ, Churg A, Roggli VL (2004). Ferruginous bodies: implications in the mechanism of fibre and particle toxicity. *Toxicol Pathol*, 32: 643–649. doi:10.1080/01926230490885733 PMID:15513907
- Ghio AJ, Kadiiska MB, Xiang QH, Mason RP (1998). In vivo evidence of free radical formation after asbestos instillation: an ESR spin trapping investigation. *Free Radic Biol Med*, 24: 11–17. doi:10.1016/S0891-5849(97)00063-4 PMID:9436609
- Ghio AJ, LeFurgey A, Roggli VL (1997). In vivo accumulation of iron on crocidolite is associated with decrements in oxidant generation by the fibre. *J Toxicol Environ Health*, 50: 125–142. doi:10.1080/009841097160537 PMID:9048957
- Ghio AJ, Stonehuerner J, Richards J, Devlin RB (2008). Iron homeostasis in the lung following asbestos exposure. *Antioxid Redox Signal*, 10: 371–377. doi:10.1089/ars.2007.1909 PMID:17999626
- Ghio AJ, Zhang J, Piantadosi CA (1992). Generation of hydroxyl radical by crocidolite asbestos is proportional to surface [Fe³⁺]. [Fe³⁺]/*Arch Biochem Biophys*, 298: 646–650. doi:10.1016/0003-9861(92)90461-5 PMID:1329664
- Gibbs AR, Stephens M, Griffiths DM *et al.* (1991). Fibre distribution in the lungs and pleura of subjects with asbestos related diffuse pleural fibrosis. *Br J Ind Med*, 48: 762–770. PMID:1659443
- Gibbs GW & Hwang CY (1975). Physical parameters of airborne asbestos fibres in various work environments—preliminary findings. *Am Ind Hyg Assoc J*, 36: 459–466. PMID:1229888
- Gibbs GW & Hwang CY (1980). Dimensions of airborne asbestos fibres. *IARC Sci Publ*, 30: 69–78. PMID:7239672
- Glickman LT, Domanski LM, Maguire TG *et al.* (1983). Mesothelioma in pet dogs associated with exposure of their owners to asbestos. *Environ Res*, 32: 305–313. doi:10.1016/0013-9351(83)90114-7 PMID:6641667
- Gloyne SR (1935). Two cases of squamous carcinoma of the lung occurring in asbestosis. *Tubercle*, 17: 5–10. doi:10.1016/S0041-3879(35)80795-2
- Goldberg MS, Parent ME, Siemiatycki J *et al.* (2001). A case-control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. *Am J Ind Med*, 39: 531–546. doi:10.1002/ajim.1052 PMID:11385637
- Goldstein B & Coetzee FS (1990). Experimental malignant mesothelioma in baboons. *Suid-Afr. Tydskrift voor Wetenskap*, 86: 89–93.
- Goldstein B, Rendall RE, Webster I (1983). A comparison of the effects of exposure of baboons to crocidolite and fibrous-glass dusts. *Environ Res*, 32: 344–359. doi:10.1016/0013-9351(83)90117-2 PMID:6315390
- Goodman M, Morgan RW, Ray R *et al.* (1999). Cancer in asbestos-exposed occupational cohorts: a meta-analysis. *Cancer Causes Control*, 10: 453–465. doi:10.1023/A:1008980927434 PMID:10530617
- Gordon GJ, Jensen RV, Hsiao LL *et al.* (2002). Translation of microarray data into clinically relevant cancer diagnostic tests using gene expression ratios in lung cancer and mesothelioma. *Cancer Res*, 62: 4963–4967. PMID:12208747
- Graham J & Graham R (1967). Ovarian cancer and asbestos. *Environ Res*, 1: 115–128. doi:10.1016/0013-9351(67)90008-4 PMID:5628974
- Greillier L, Baas P, Welch JJ *et al.* (2008). Biomarkers for malignant pleural mesothelioma: current status. *Mol Diagn Ther*, 12: 375–390. PMID:19035624
- Gronow JR (1987). The dissolution of asbestos fibres in water. *Clay Miner*, 22: 21–35. doi:10.1180/claymin.1987.022.1.03
- Gross P, DeTreville RT, Tolker EB *et al.* (1967). Experimental asbestosis. The development of lung cancer in rats with pulmonary deposits of chrysotile asbestos dust. *Arch Environ Health*, 15: 343–355. PMID:6035084
- Gulumian M (1999). The ability of mineral dusts and fibres to initiate lipid peroxidation. Part I: parameters which determine this ability. *Redox Rep*, 4: 141–163. doi:10.1179/135100099101534855 PMID:10658820
- Gulumian M (2005). An update on the detoxification processes for silica particles and asbestos fibres: successes and limitations. *J Toxicol Environ Health B Crit Rev*, 8: 453–483. doi:10.1080/10937400590952547 PMID:16188731
- Gulumian M, Bhoolia DJ, Du Toit RS *et al.* (1993a). Activation of UICC crocidolite: the effect of conversion of some ferric ions to ferrous ions. *Environ Res*, 60: 193–206. doi:10.1006/enrs.1993.1027 PMID:8386081
- Gulumian M, Bhoolia DJ, Theodorou P *et al.* (1993b). Parameters Which Determine the Activity of the Transition-Metal Iron in Crocidolite Asbestos - ESR, Mossbauer Spectroscopic and Iron Mobilization Studies. *S Afr J Sci*, 89: 405–409.
- Haegens A, van der Vliet A, Butnor KJ *et al.* (2005). Asbestos-induced lung inflammation and epithelial cell proliferation are altered in myeloperoxidase-null mice. *Cancer Res*, 65: 9670–9677. doi:10.1158/0008-5472.CAN-05-1751 PMID:16266986
- Hagemeyer O, Otten H, Kraus T (2006). Asbestos consumption, asbestos exposure and asbestos-related occupational diseases in Germany. *Int Arch Occup*

IARC MONOGRAPHS – 100C

- Environ Health*, 79: 613–620. doi:10.1007/s00420-006-0091-x PMID:16523318
- Hardy JA & Aust AE (1995). Iron in asbestos chemistry and carcinogenicity. *Chem Rev*, 95: 97–118. doi:10.1021/cr00033a005
- Health and Safety Executive (2005). *HSG 248 'Asbestos: The analysts' guide for sampling, analysis and clearance procedures'*. London: HSE Books.
- Health Effects Institute (1991). *Asbestos in public and commercial buildings: A literature review and synthesis of current knowledge*. Cambridge, Massachusetts: Health Effects Institute-Asbestos Research.
- Hein MJ, Stayner LT, Lehman E, Dement JM (2007). Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med*, 64: 616–625. doi:10.1136/oem.2006.031005 PMID:17449563
- Heineman EF, Bernstein L, Stark AD, Spirtas R (1996). Mesothelioma, asbestos, and reported history of cancer in first-degree relatives. *Cancer*, 77: 549–554. doi:10.1002/(SICI)1097-0142(19960201)77:3<549::AID-CNCR18>3.0.CO;2-4 PMID:8630964
- Heller DS, Gordon RE, Westhoff C, Gerber S (1996). Asbestos exposure and ovarian fibre burden. *Am J Ind Med*, 29: 435–439. doi:10.1002/(SICI)1097-0274(199605)29:5<435::AID-AJIM1>3.0.CO;2-L PMID:8732916
- Hesterberg TW, Axten C, McConnell EE *et al.* T. W. Hesterberg, C. Axten, E. E. M (1999). Studies on the inhalation toxicology of two fibreglasses and amosite asbestos in the syrian golden hamster. Part I. Results of a subchronic study and dose selection for a chronic study. *Inhal Toxicol*, 11: 747–784. doi:10.1080/089583799196745 PMID:10477658
- Hesterberg TW, Chase G, Axten C *et al.* (1998a). Biopersistence of synthetic vitreous fibres and amosite asbestos in the rat lung following inhalation. *Toxicol Appl Pharmacol*, 151: 262–275. doi:10.1006/taap.1998.8472 PMID:9707503
- Hesterberg TW, Hart GA, Chevalier J *et al.* (1998b). The importance of fibre biopersistence and lung dose in determining the chronic inhalation effects of X607, RCF1, and chrysotile asbestos in rats. *Toxicol Appl Pharmacol*, 153: 68–82. doi:10.1006/taap.1998.8522 PMID:9875301
- Hesterberg TW, Miiller WC, McConnell EE *et al.* (1993). Chronic inhalation toxicity of size-separated glass fibres in Fischer 344 rats. *Fundam Appl Toxicol*, 20: 464–476. doi:10.1006/faat.1993.1057 PMID:8390950
- Hesterberg TW, Miiller WC, Musselman RP *et al.* (1996). Biopersistence of Man-Made Vitreous Fibres and Crocidolite Asbestos in the Rat Lung Following Inhalation. *Fundam Appl Toxicol*, 29: 267–279. doi:10.1006/faat.1996.0031 PMID:8812275
- Higashi T, Hori H, Sakurai H *et al.* (1994). Work environment of plants manufacturing asbestos-containing products in Japan. *Ann Occup Hyg*, 38: 489–494, 409. doi:10.1093/annhyg/38.4.489 PMID:7978970
- Hill IM, Beswick PH, Donaldson K (1995). Differential release of superoxide anions by macrophages treated with long and short fibre amosite asbestos is a consequence of differential affinity for opsonin. *Occup Environ Med*, 52: 92–96. doi:10.1136/oem.52.2.92 PMID:7757173
- Hill RJ, Edwards RE, Carthew P (1990). Early changes in the pleural mesothelium following intrapleural inoculation of the mineral fibre erionite and the subsequent development of mesotheliomas. *J Exp Pathol (Oxford)*, 71: 105–118. PMID:2155636
- Hilt B, Langård S, Andersen A, Rosenberg J (1985). Asbestos exposure, smoking habits, and cancer incidence among production and maintenance workers in an electrochemical plant. *Am J Ind Med*, 8: 565–577. doi:10.1002/ajim.4700080608 PMID:3000174
- Hobson J, Wright JL, Churg A (1990). Active oxygen species mediate asbestos fibre uptake by tracheal epithelial cells. *FASEB J*, 4: 3135–3139. PMID:2170219
- Hodgson JT & Darnton A (2000). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg*, 44: 565–601. PMID:11108782
- Hodgson JT & Jones RD (1986). Mortality of asbestos workers in England and Wales 1971–81. *Br J Ind Med*, 43: 158–164. PMID:3947577
- Homa DM, Garabrant DH, Gillespie BW (1994). A meta-analysis of cancer of the colorectum and asbestos exposure. *Am J Epidemiol*, 139: 1210–1222. PMID:8209879
- Howe HL, Wolfgang PE, Burnett WS *et al.* (1989). Cancer incidence following exposure to drinking water with asbestos leachate. *Public Health Rep*, 104: 251–256. PMID:2498974
- Hume LA & Rimstidt JD (1992). The biodegradability of chrysotile asbestos. *Am Mineral*, 77: 1125–1128.
- IARC (1973). Some inorganic and organometallic compounds. *IARC Monogr Eval Carcinog Risk Chem Man*, 2: 1–181.
- IARC (1977). Some miscellaneous pharmaceutical substances. *IARC Monogr Eval Carcinog Risk Chem Man*, 13: 1–255. PMID:16821
- IARC (1985). Polynuclear aromatic compounds, Part 4, bitumens, coal-tars and derived products, shale-oils and soots. *IARC Monogr Eval Carcinog Risk Chem Hum*, 35: 1–247. PMID:2991123
- IARC (1986). Tobacco smoking. *IARC Monogr Eval Carcinog Risk Chem Hum*, 38: 35–394. PMID:3460963
- IARC (1987a). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203
- IARC (1987b). Silica and some silicates. *IARC Monogr Eval Carcinog Risk Chem Hum*, 42: 1–239. PMID:2824337
- IARC (1988). Alcohol Drinking. *IARC Monogr Eval Carcinog Risks Hum*, 44: 1–378. PMID:3236394

- IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49: 1-648. PMID:2232124
- IARC (1992). Occupational exposures to mists and vapours from strong inorganic acids and other industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*, 54: 1-310. PMID:1345371
- IARC (1993). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. *IARC Monogr Eval Carcinog Risks Hum*, 58: 1-415. PMID:8022054
- IARC (1997). Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils. *IARC Monogr Eval Carcinog Risks Hum*, 68: 1-475. PMID:9303953
- IARC (2000). IARC Working group on the evaluation of carcinogenic risks to humans: ionizing radiation, Part I, X- and gamma- radiation and neutrons. Lyon, France, 26 May-2 June 1999. *IARC Monogr Eval Carcinog Risks Hum*, 75: 1-448. PMID:11203346
- IARC (2001). Ionizing radiation, Part 2: some internally deposited radionuclides. *IARC Monogr Eval Carcinog Risks Hum*, 78: 1-559. PMID:11421248
- IARC (2002). Man-made vitreous fibres. *IARC Monogr Eval Carcinog Risks Hum*, 81: 1-381. PMID:12458547
- IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, 83: 1-1438. PMID:15285078
- IARC (2007). Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum*, 90: 1-636. PMID:18354839
- IARC (2010). Carbon black, titanium dioxide, and talc. *IARC Monogr Eval Carcinog Risks Hum*, 93: 1-452.
- IARC (2012c). Biological agents. *IARC Monogr Eval Carcinog Risks Hum*, 100B: PMID:18335640
- IARC (2012e). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F: PMID:18335640
- IARC (2012d). Personal habits and household exposures. *IARC Monogr Eval Carcinog Risks Hum*, 100E: PMID:18335640
- IARC (2012b). Metals, arsenic, dusts and fibres. *IARC Monogr Eval Carcinog Risks Hum*, 100C: PMID:18335640
- IARC (2012a). Radiation. *IARC Monogr Eval Carcinog Risks Hum*, 100D: PMID:18335640
- IMA (2005). Industrial Minerals Association-Europe Fact Sheet: Talc, Brussels.
- IOM (2006). Asbestos: Selected Cancers. Institute of Medicine of the National Academy of Science [http://books.nap.edu/catalog/11665.html]
- Jakobsson K, Albin M, Hagmar L (1994). Asbestos, cement, and cancer in the right part of the colon. *Occup Environ Med*, 51: 95-101. doi:10.1136/oem.51.2.95 PMID:8111470
- Jansson C, Johansson AL, Bergdahl IA *et al.* (2005). Occupational exposures and risk of esophageal and gastric cardia cancers among male Swedish construction workers. *Cancer Causes Control*, 16: 755-764. doi:10.1007/s10552-005-1723-2 PMID:16049815
- Jaurand MC (1996). Use of in-vitro genotoxicity and cell transformation assays to evaluate the potential carcinogenicity of fibres. *IARC Sci Publ*, 55-72. PMID:9101317
- Jehan N (1984) *Sustainable management of mineral resources with special reference to asbestos and silica in northern Pakistan*. Ph.D., National Centre of Excellence in Geology, University of Peshawar.
- Kamp DW & Weitzman SA (1999). The molecular basis of asbestos induced lung injury. *Thorax*, 54: 638-652. doi:10.1136/thx.54.7.638 PMID:10377212
- Kane AB (2006). Animal models of malignant mesothelioma. *Inhal Toxicol*, 18: 1001-1004. doi:10.1080/08958370600835393 PMID:16920675
- Kang SK, Burnett CA, Freund E *et al.* (1997). Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures. *Am J Ind Med*, 31: 713-718. doi:10.1002/(SICI)1097-0274(199706)31:6<713::AID-AJIM7>3.0.CO;2-R PMID:9131226
- Karjalainen A, Pukkala E, Kauppinen T, Partanen T (1999). Incidence of cancer among Finnish patients with asbestos-related pulmonary or pleural fibrosis. *Cancer Causes Control*, 10: 51-57. doi:10.1023/A:1008845332422 PMID:10334642
- Kauppinen T & Korhonen K (1987). Exposure to asbestos during brake maintenance of automotive vehicles by different methods. *Am Ind Hyg Assoc J*, 48: 499-504. PMID:3591672
- Kimura K (1987). [Asbestos and environment.] *Dig Sci Lab*, 42: 4-13.
- Kjærheim K, Ulvestad B, Martinsen JI, Andersen A (2005). Cancer of the gastrointestinal tract and exposure to asbestos in drinking water among lighthouse keepers (Norway). *Cancer Causes Control*, 16: 593-598. doi:10.1007/s10552-004-7844-1 PMID:15986115
- Kleymenova EV, Horesovsky G, Pylev LN, Everitt J (1999). Mesotheliomas induced in rats by the fibrous mineral erionite are independent from p53 alterations. *Cancer Lett*, 147: 55-61. doi:10.1016/S0304-3835(99)00275-X PMID:10660089
- Kogan FM, Vanchugova NN, Frasci VN (1987). Possibility of inducing glandular cancer of the stomach in rats exposed to asbestos. *Br J Ind Med*, 44: 682-686. PMID:3676121
- Kratzke RA, Gazdar AF (2005). *Oncogenes and tumor suppressor genes in malignant mesothelioma*. In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies*. Pass HI, Vogelzang NJ Carbone M, editors. New York: Springer Science & Business Media, Inc., pp. 124-141.
- Krstev S, Dosemeci M, Lissowska J *et al.* (2005). Occupation and risk of cancer of the stomach in Poland. *Occup Environ Med*, 62: 318-324. doi:10.1136/oem.2004.015883 PMID:15837853

IARC MONOGRAPHS – 100C

- Landrigan PJ, Lioy PJ, Thurston G *et al.* NIEHS World Trade Center Working Group (2004). Health and environmental consequences of the world trade center disaster. *Environ Health Perspect*, 112: 731–739. PMID:15121517
- Langer AM & Nolan RP (1994). Chrysotile: its occurrence and properties as variables controlling biological effects. *Ann Occup Hyg*, 38: 427–51. PMID:7978965
- Langseth H, Johansen BV, Nesland JM, Kjaerheim K (2007). Asbestos fibres in ovarian tissue from Norwegian pulp and paper workers. *Int J Gynecol Cancer*, 17: 44–49. doi:10.1111/j.1525-1438.2006.00768.x PMID:17291230
- Langseth H & Kjaerheim K (2004). Ovarian cancer and occupational exposure among pulp and paper employees in Norway. *Scand J Work Environ Health*, 30: 356–361. PMID:15529799
- Lash TL, Crouch EA, Green LC (1997). A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. *Occup Environ Med*, 54: 254–263. doi:10.1136/oem.54.4.254 PMID:9166131
- Le Bouffant L, Daniel H, Henin JP *et al.* (1987). Experimental study on long-term effects of inhaled MMMF on the lungs of rats. *Ann Occup Hyg*, 31: 4B765–790. doi:10.1093/annhyg/31.4B.765 PMID:3450235
- Lee KP, Barras CE, Griffith FD *et al.* (1981). Comparative pulmonary responses to inhaled inorganic fibres with asbestos and fibreglass. *Environ Res*, 24: 167–191. doi:10.1016/0013-9351(81)90143-2 PMID:6260477
- Lee KP, Reinhardt CF (1984). *Biological studies on inorganic potassium titanate fibres*. In: *Biological Effects Man-Made Mineral Fibres: Proceedings of a WHO/IARC Conference in Association with JEMRB and TIMA*. Copenhagen: World Health Organization, Regional Office for Europe, 323–333.
- Levy BS, Sigurdson E, Mandel J *et al.* (1976). Investigating possible effects of asbestos in city water: surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. *Am J Epidemiol*, 103: 362–368. PMID:1258862
- Liddell FD, McDonald AD, McDonald JC (1997). The 1891–1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. *Ann Occup Hyg*, 41: 13–36. PMID:9072947
- Lindor NM, Lindor CY, Greene MH (2006). *Hereditary neoplastic syndromes*. In: *Cancer Epidemiology and Prevention*, 3rd ed. Schottenfeld D, Fraumeni JF, Jr., editors. New York: Oxford University Press, pp. 562–576.
- Lippmann M (1990). Effects of fibre characteristics on lung deposition, retention, and disease. *Environ Health Perspect*, 88: 311–317. doi:10.2307/3431093 PMID:2272328
- Lippmann M, Yeates DB, Albert RE (1980). Deposition, retention, and clearance of inhaled particles. *Br J Ind Med*, 37: 337–362. PMID:7004477
- Loomis D, Dement JM, Richardson D, Wolf S (2009). Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. *Occup Environ Med*, 67: 580–584. doi:10.1136/oem.2008.044362 PMID:19897464
- López-Ríos F, Chuai S, Flores R *et al.* (2006). Global gene expression profiling of pleural mesotheliomas: over-expression of aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction. *Cancer Res*, 66: 2970–2979. doi:10.1158/0008-5472.CAN-05-3907 PMID:16540645
- Lu J, Keane MJ, Ong T, Wallace WE (1994). In vitro genotoxicity studies of chrysotile asbestos fibres dispersed in simulated pulmonary surfactant. *Mutat Res*, 320: 253–259. doi:10.1016/0165-1218(94)90078-7 PMID:7508551
- Luce D, Bugel I, Goldberg P *et al.* (2000). Environmental exposure to tremolite and respiratory cancer in New Caledonia: a case-control study. *Am J Epidemiol*, 151: 259–265. PMID:10670550
- Lund LG, Williams MG, Dodson RF, Aust AE (1994). Iron associated with asbestos bodies is responsible for the formation of single strand breaks in phi X174 RFI DNA. *Occup Environ Med*, 51: 200–204. doi:10.1136/oem.51.3.200 PMID:8130850
- Lynch KM & Smith WA (1935). Pulmonary asbestosis III: Carcinoma of the lung in asbeto-silicosis. *Am J Cancer*, 24: 56–64.
- Madl AK, Clark K, Paustenbach DJ (2007). Exposure to airborne asbestos during removal and installation of gaskets and packings: a review of published and unpublished studies. *J Toxicol Environ Health, Part B*, 10: 259–286.
- Magnani C, Agudo A, González CA *et al.* (2000). Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. *Br J Cancer*, 83: 104–111. PMID:10883677
- Magnani C, Dalmasso P, Biggeri A *et al.* (2001). Increased risk of malignant mesothelioma of the pleura after residential or domestic exposure to asbestos: a case-control study in Casale Monferrato, Italy. *Environ Health Perspect*, 109: 915–919. doi:10.2307/3454992 PMID:11673120
- Magnani C, Ferrante D, Barone-Adesi F *et al.* (2008). Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med*, 65: 164–170. doi:10.1136/oem.2007.032847 PMID:17704197
- Maltoni C, Minardi F (1989). *Recent results of carcinogenicity bioassays of fibres and other particulate materials*. In: *Non-occupational Exposure to Mineral Fibres*. IARC Scientific Publ. Vol. 90. Bignon J, Peto J Saracci R, editors. Lyon: International Agency for Research on Cancer, pp. 46–53.
- Manning CB, Vallyathan V, Mossman BT (2002). Diseases caused by asbestos: mechanisms of injury and disease

- development. *Int Immunopharmacol*, 2: 191–200. doi:10.1016/S1567-5769(01)00172-2 PMID:11811924
- Marchand JL, Luce D, Leclerc A *et al.* (2000). Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibres: results of a case-control study. *Am J Ind Med*, 37: 581–589. doi:10.1002/(SICI)1097-0274(200006)37:6<581::AID-AJIM2>3.0.CO;2-D PMID:10797501
- Marsh GM (1983). Critical review of epidemiologic studies related to ingested asbestos. *Environ Health Perspect*, 53: 49–56. doi:10.1289/ehp.835349 PMID:6662094
- Martra G, Tomatis M, Fenoglio I *et al.* (2003). Ascorbic acid modifies the surface of asbestos: possible implications in the molecular mechanisms of toxicity. *Chem Res Toxicol*, 16: 328–335. doi:10.1021/tx0200515 PMID:12641433
- McConnell EE, Axten C, Hesterberg TW *et al.* (1999). Studies on the inhalation toxicology of two fibre-glasses and amosite asbestos in the Syrian golden hamster. Part II. Results of chronic exposure. *Inhal Toxicol*, 11: 785–835. doi:10.1080/089583799196754 PMID:10477659
- McConnell EE, Hall L, Adkins B (1991). Studies on the chronic toxicity (inhalation) of wollastonite in Fischer 344 rats. *Inhal Toxicol*, 3: 323–337. doi:10.3109/08958379109145292
- McConnell EE, Kamstrup O, Musselman R *et al.* (1994). Chronic inhalation study of size-separated rock and slag wool insulation fibres in Fischer 344/N rats. *Inhal Toxicol*, 6: 571–614. doi:10.3109/08958379409003042
- McConnell EE, Wagner JC, Skidmore J *et al.* (1984). A comparative study of the fibrogenic and carcinogenic effects of UICC Canadian chrysotile B asbestos and glass microfibre (JM 100). In: *Proceedings of a WHO/IARC Conference in Association with JEMRB and TIMA, Copenhagen, 20 - 22 April, 1982 Biological Effects of Man-Made Mineral Fibres*. Copenhagen: WHO Regional Office for Europe, pp. 234–252.
- McConnochie K, Simonato L, Mavrides P *et al.* (1987). Mesothelioma in Cyprus: the role of tremolite. *Thorax*, 42: 342–347. doi:10.1136/thx.42.5.342 PMID:2821642
- McDonald AD, Case BW, Churg A *et al.* (1997). Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. *Ann Occup Hyg*, 41: 707–719. PMID:9375529
- McDonald AD, Fry JS, Woolley AJ, McDonald J (1983). Dust exposure and mortality in an American chrysotile textile plant. *Br J Ind Med*, 40: 361–367. PMID:6313032
- McDonald JC (1998). Mineral fibre persistence and carcinogenicity. *Ind Health*, 36: 372–375. doi:10.2486/indhealth.36.372 PMID:9810152
- McDonald JC, Harris J, Armstrong B (2004). Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. *Occup Environ Med*, 61: 363–366. doi:10.1136/oem.2003.008649 PMID:15031396
- McDonald JC, Liddell FD, Dufresne A, McDonald AD (1993). The 1891–1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976–88. *Br J Ind Med*, 50: 1073–1081. PMID:8280638
- McDonald JC, Liddell FD, Gibbs GW *et al.* (1980). Dust exposure and mortality in chrysotile mining, 1910–75. *Br J Ind Med*, 37: 11–24. PMID:7370189
- McDonald JC & McDonald AD (1995). Chrysotile, tremolite, and mesothelioma. *Science*, 267: 776–777. PMID:7710525
- McDonald JC & McDonald AD (1997). Chrysotile, tremolite and carcinogenicity. *Ann Occup Hyg*, 41: 699–705. PMID:9375528
- McFadden D, Wright JL, Wiggs B, Churg A (1986). Smoking inhibits asbestos clearance. *Am Rev Respir Dis*, 133: 372–374. PMID:2869726
- Meeker GP, Bern AM, Brownfield IK *et al.* (2003). The composition and morphology of amphiboles from the Rainy Creek complex, near Libby, Montana. *Am Mineralogist*, 88: 1955–1969.
- Meurman LO, Kiviluoto R, Hakama M (1974). Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland. *Br J Ind Med*, 31: 105–112. PMID:4830762
- Mirabelli D, Calisti R, Barone-Adesi F *et al.* (2008). Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy. *Occup Environ Med*, 65: 815–819. doi:10.1136/oem.2007.037689 PMID:18524838
- Monchaux G, Bignon J, Jaurand MC *et al.* (1981). Mesotheliomas in rats following inoculation with acid-leached chrysotile asbestos and other mineral fibres. *Carcinogenesis*, 2: 229–236. doi:10.1093/carcin/2.3.229 PMID:6268324
- Morgan A (1997). Acid leaching studies of chrysotile asbestos from mines in the Coalinga region of California and from Quebec and British Columbia. *Ann Occup Hyg*, 41: 249–268. PMID:9204753
- Morgan RW, Foliart DE, Wong O (1985). Asbestos and gastrointestinal cancer. A review of the literature. *West J Med*, 143: 60–65. PMID:4036114
- Muhle H, Pott F, Bellmann B *et al.* (1987). Inhalation and injection experiments in rats to test the carcinogenicity of MMMF. *Ann Occup Hyg*, 31: 4B755–764. doi:10.1093/annhyg/31.4B.755 PMID:2835926
- Murthy SS & Testa JR (1999). Asbestos, chromosomal deletions, and tumor suppressor gene alterations in human malignant mesothelioma. *J Cell Physiol*, 180: 150–157. doi:10.1002/(SICI)1097-4652(199908)180:2<150::AID-JCP2>3.0.CO;2-H PMID:10395284
- Murthy SS, Shen T, De Rienzo A *et al.* (2000). Expression of GPC3, an X-linked recessive overgrowth gene, is silenced in malignant mesothelioma. *Oncogene*, 19: 410–416. doi:10.1038/sj.onc.1203322 PMID:10656689
- Musk AW, de Klerk NH, Reid A *et al.* (2008). Mortality of former crocidolite (blue asbestos) miners and millers

IARC MONOGRAPHS – 100C

- at Wittenoom. *Occup Environ Med*, 65: 541–543. doi:10.1136/oem.2007.034280 PMID:18045848
- Mzileni O, Sitas F, Steyn K *et al.* (1999). Lung cancer, tobacco, and environmental factors in the African population of the Northern Province, South Africa. *Tob Control*, 8: 398–401. doi:10.1136/tc.8.4.398 PMID:10629246
- National Academy of Sciences (1993). Available at: <http://www.nasonline.org>
- NTP (1983). NTP Lifetime Carcinogenesis Studies of Amosite Asbestos (CAS No. 12172–73–5) in Syrian Golden Hamsters (Feed Studies). *Natl Toxicol Program Tech Rep Ser*, 249: 1–81. PMID:12748679
- NTP (1985). NTP Toxicology and Carcinogenesis Studies of Chrysotile Asbestos (CAS No. 12001–29–5) in F344/N Rats (Feed Studies). *Natl Toxicol Program Tech Rep Ser*, 295: 1–390. PMID:12748710
- NTP (1988). NTP Toxicology and Carcinogenesis Studies of Crocidolite Asbestos (CAS No. 12001–28–4) In F344/N Rats (Feed Studies). *Natl Toxicol Program Tech Rep Ser*, 280: 1–178. PMID:12748699
- NTP (1990a). NTP Toxicology and Carcinogenesis Studies of Amosite Asbestos (CAS No. 12172–73–5) in F344/N Rats (Feed Studies). *Natl Toxicol Program Tech Rep Ser*, 279: 1–341. PMID:12748700
- NTP (1990b). Toxicology and Carcinogenesis Studies of Chrysotile Asbestos (CAS No. 12001–29–5) in Syrian Golden Hamsters (Feed Studies). *Natl Toxicol Program Tech Rep Ser*, 246: 1–390. PMID:12750747
- NTP (1990c). NTP Toxicology and Carcinogenesis Studies of Tremolite (CAS No. 14567–73–8) in F344/N Rats (Feed Studies). *Natl Toxicol Program Tech Rep Ser*, 277: 1–183. PMID:12748702
- NTP (2005). NTP 11th Report on Carcinogens. *Rep Carcinog*, 111–A32. PMID:19826456
- Nelson HH, Christiani DC, Wiencke JK *et al.* (1999). k-ras mutation and occupational asbestos exposure in lung adenocarcinoma: asbestos-related cancer without asbestosis. *Cancer Res*, 59: 4570–4573. PMID:10493509
- Nelson HH & Kelsey KT (2002). The molecular epidemiology of asbestos and tobacco in lung cancer. *Oncogene*, 21: 7284–7288. doi:10.1038/sj.onc.1205804 PMID:12379872
- Newhouse ML, Berry G, Wagner JC, Turok ME (1972). A study of the mortality of female asbestos workers. *Br J Ind Med*, 29: 134–141. PMID:5021993
- NIOSH (1990). National Occupational Exposure Survey. Estimated Numbers of Employees Potentially Exposed to Talc by 2-Digit Standard Industrial Classification (SIC). Available at: <http://www.cdc.gov/noes/default.html>
- NIOSH (2002a). Work-Related Lung Disease Surveillance Report (DHHS Publication No. 2003–111), Cincinnati, OH.
- NIOSH (2002b). Comments of the National Institute for Occupational Safety and Health on the Mine Safety and Health Administration Advanced Notice of Proposed Rulemaking on Measuring and Controlling Asbestos Exposure.
- NIOSH (2008). Current Intelligence Bulletin (June 2008-Revised Draft) Asbestos and Other Elongated Mineral Particles: State of the Science and Roadmap for Research.
- NIOSH (2009). Asbestos fibres and other elongated mineral particles: state of the science and roadmap for research Report. Department of Health and Human Services, Public Health Service, Centers for Disease Control.
- Nishikawa K, Takahashi K, Karjalainen A *et al.* (2008). Recent mortality from pleural mesothelioma, historical patterns of asbestos use, and adoption of bans: a global assessment. *Environ Health Perspect*, 116: 1675–1680. doi:10.1289/ehp.11272 PMID:19079719
- Noonan CW, Pfau JC, Larson TC, Spence MR (2006). Nested case-control study of autoimmune disease in an asbestos-exposed population. *Environ Health Perspect*, 114: 1243–1247. doi:10.1289/ehp.9203 PMID:16882533
- Nymark P, Wikman H, Hienonen-Kempas T, Anttila S (2008). Molecular and genetic changes in asbestos-related lung cancer. *Cancer Lett*, 265: 1–15. doi:10.1016/j.canlet.2008.02.043 PMID:18364247
- Oestenstad K, Honda Y, Delzell E, Brill I (2002). Assessment of historical exposures to talc at a mining and milling facility. *Ann Occup Hyg*, 46: 587–596. doi:10.1093/annhyg/mef076 PMID:12270883
- Olshan AF (2006). *Cancer of the larynx*. In: *Cancer Epidemiology and Prevention*, 3rd ed. Schottenfeld D, Fraumeni JF, Jr., editors. New York: Oxford University Press, pp. 627–638.
- OSHA (1990). Occupational Exposure to Asbestos, Tremolite, Anthophyllite and Actinolite - Proposed Rulemaking (Supplemental) and Notice of Hearing U.S. Department of Labor, Occupational Safety and Health Administration. *Fed Regist*, 55: 29712–29753.
- OSHA (2008) Safety and Health Topics: Asbestos. Available at: <http://www.osha.gov/SLTC/asbestos/index.html>
- Otero Areán C, Barcelo F, Fubini B (1999). Free radical activity of mineral fibres containing adsorbed ferritin: Detection using supercoiled DNA. *Res Chem Intermed*, 25: 177–185. doi:10.1163/156856799X00284
- Pan XL, Day HW, Wang W *et al.* (2005). Residential proximity to naturally occurring asbestos and mesothelioma risk in California. *Am J Respir Crit Care Med*, 172: 1019–1025. doi:10.1164/rccm.200412-1731OC PMID:15976368
- Pang ZC, Zhang Z, Wang Y, Zhang H (1997). Mortality from a Chinese asbestos plant: overall cancer mortality. *Am J Ind Med*, 32: 442–444. doi:10.1002/(SICI)1097-0274(199711)32:5<442::AID-AJIM2>3.0.CO;2-U PMID:9327066

- Parent ME, Siemiatycki J, Fritschi L (2000). Workplace exposures and cancer of the oesophagus. *Occup Environ Med*, 57: 325–334. doi:10.1136/oem.57.5.325 PMID:10769298
- Pass HI, Lott D, Lonardo F *et al.* (2005). Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. *N Engl J Med*, 353: 1564–1573. doi:10.1056/NEJMoa051185 PMID:16221779
- Paustenbach DJ, Finley BL, Lu ET *et al.* (2004). Environmental and occupational health hazards associated with the presence of asbestos in brake linings and pads (1900 to present): A “state-of-the-art” review. *J Toxicol Environ Health, Part B*, 7: 125–80.. PMID:14681081.
- Peto J, Doll R, Hermon C *et al.* (1985). Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann Occup Hyg*, 29: 305–355. doi:10.1093/annhyg/29.3.305 PMID:4073702
- Pfeifer GP, Denissenko MF, Olivier M *et al.* (2002). Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene*, 21: 7435–7451. doi:10.1038/sj.onc.1205803 PMID:12379884
- Pigott GH & Ishmael J (1982). A strategy for the design and evaluation of a ‘safe’ inorganic fibre. *Ann Occup Hyg*, 26: 371–380. doi:10.1093/annhyg/26.2.371 PMID:7181277
- Pigott GH & Ishmael J (1992). The effects of intrapleural injections of alumina and aluminosilicate (ceramic) fibres. *Int J Exp Pathol*, 73: 137–146. PMID:1571274
- Piolatto G, Negri E, La Vecchia C *et al.* (1990). An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. *Br J Ind Med*, 47: 810–814. PMID:2176805
- Pira E, Pelucchi C, Buffoni L *et al.* (2005). Cancer mortality in a cohort of asbestos textile workers. *Br J Cancer*, 92: 580–586. doi:10.1038/sj.bjc.6602240 PMID:15702125
- Polissar L, Severson RK, Boatman ES, Thomas DB (1982). Cancer incidence in relation to asbestos in drinking water in the Puget Sound region. *Am J Epidemiol*, 116: 314–328. PMID:7114040
- Pooley FD (1976). An examination of the fibrous mineral content of asbestos lung tissue from the Canadian chrysotile mining industry. *Environ Res*, 12: 281–298. doi:10.1016/0013-9351(76)90038-4 PMID:1001300
- Pott F (1993). *Testing the carcinogenicity of fibres in laboratory animals: Results and conclusions.* In: *Fibre Toxicology*. Warheit DB, editor. Academic Press, pp. 395–424.
- Pott F, Roller M (1993a). *Relevance of non-physiologic exposure routes for carcinogenicity studies of solid particles.* In: *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. 4th International Inhalation Symposium Hanover 1 - 5 March, 1993.* Mohr U, editor. Washington, D.C.: ILSI-Press, pp. 109–125.
- Pott F, Roller M (1993b). *Die krebserzeugende Wirkung von Fasern unter besonderer Berücksichtigung der Inhalationsversuche.*, Dortmund: Bundesanstalt für Arbeitsschutz, No. 1217.
- Pott F, Roller M, Althoff GH (1995). *Krebsrisiko durch Fasern - ein zusammenfassender Vergleich von epidemiologischen und tierexperimentellen Daten.* In: *Ges. z. Förderung d. Lufthygiene u. Silikoseforschung e.V. Düsseldorf: Umwelthygiene, Bd 27. Medizinisches Institut für Umwelthygiene, Jahresbericht 1994/1995, 133–200.* Stefan W. Albers, Düsseldorf, 1995
- Pott F, Roller M, Ziem U *et al.* (1989). Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. *IARC Sci Publ*, 90: 173–179. PMID:2744824
- Pott F, Ziem U, Mohr U (1984). *Lung carcinomas and mesotheliomas following intratracheal instillation of glass fibres and asbestos.* In: *Proceedings of the VIth International Pneumoconiosis Conference 20–23 September 1983.* Bochum, Germany: International Labour Office, pp. 746–756.
- Pott F, Ziem U, Reiffer FJ *et al.* (1987). Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Exp Pathol*, 32: 129–152. PMID:3436395
- Price B, Crump KS, Baird EC 3rd (1992). Airborne asbestos levels in buildings: maintenance worker and occupant exposures. *J Expo Anal Environ Epidemiol*, 2: 357–374. PMID:1422164
- Pukkala E, Martinsen JI, Lynge E *et al.* (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol*, 48: 646–790. doi:10.1080/02841860902913546 PMID:19925375
- Puntoni R, Vercelli M, Merlo F *et al.* (1979). Mortality among shipyard workers in Genoa, Italy. *Ann NY Acad Sci*, 330: 1 Health Hazard 353–377. doi:10.1111/j.1749-6632.1979.tb18738.x PMID:230774
- Putzu MG, Bruno C, Zona A *et al.* (2006). Fluoro-edenitic fibres in the sputum of subjects from Biancavilla (Sicily): a pilot study. *Environ Health*, 5: 20 doi:10.1186/1476-069X-5-20 PMID:16780574
- Raffn E, Lynge E, Juel K, Korsgaard B (1989). Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *Br J Ind Med*, 46: 90–96. PMID:2923830
- Raffn E, Villadsen E, Lynge E (1996). Cancer of the colorectum in asbestos cement workers in Denmark. *Am J Ind Med*, 30: 267–272. doi:10.1002/(SICI)1097-0274(199609)30:3<267::AID-AJIM3>3.0.CO;2-W PMID:8876793
- Rees D, du Toit RSJ, Rendal REG *et al.* (1992). Tremolite in Southern African chrysotile. *S Afr J Sci*, 88: 468–469.
- Rees D, Myers JE, Goodman K *et al.* (1999). Case-control study of mesothelioma in South Africa. *Am J Ind Med*, 35: 213–222. doi:10.1002/(SICI)1097-0274(199903)35:3<213::AID-AJIM1>3.0.CO;2-R PMID:9987554
- Reeves AL, Puro HE, Smith RG (1974). Inhalation carcinogenesis from various forms of asbestos. *Environ*

IARC MONOGRAPHS – 100C

- Res, 8: 178–202. doi:10.1016/0013-9351(74)90050-4 PMID:4455505
- Reid A, Ambrosini G, de Klerk N *et al.* (2004). Aerodigestive and gastrointestinal tract cancers and exposure to crocidolite (blue asbestos): incidence and mortality among former crocidolite workers. *Int J Cancer*, 111: 757–761. doi:10.1002/ijc.20313 PMID:15252847
- Reid A, Heyworth J, de Klerk N, Musk AW (2008). The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. *Occup Environ Med*, 65: 743–749. doi:10.1136/oem.2007.035782 PMID:18940957
- Reid A, Segal A, Heyworth JS *et al.* (2009). Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. *Cancer Epidemiol Biomarkers Prev*, 18: 140–147. doi:10.1158/1055-9965.EPI-08-0746 PMID:19124491
- Rice C & Heineman EF (2003). An asbestos job exposure matrix to characterize fibre type, length, and relative exposure intensity. *Appl Occup Environ Hyg*, 18: 506–512. doi:10.1080/10473220301459 PMID:12791547
- Riganti C, Aldieri E, Bergandi L *et al.* (2003). Long and short fibre amosite asbestos alters at a different extent the redox metabolism in human lung epithelial cells. *Toxicol Appl Pharmacol*, 193: 106–115. doi:10.1016/S0041-008X(03)00339-9 PMID:14613721
- Roberts WL, Rapp GR Jr, Weber J (1974). *Encyclopedia of Minerals*. New York: Van Nostrand Reinhold, pp. 601.
- Robinson BW, Creaney J, Lake R *et al.* (2005). Soluble mesothelin-related protein—a blood test for mesothelioma. *Lung Cancer*, 49: Suppl 1S109–S111. doi:10.1016/j.lungcan.2005.03.020 PMID:15950789
- Roggli VL (1990). Human disease consequences of fibre exposures: a review of human lung pathology and fibre burden data. *Environ Health Perspect*, 88: 295–303. doi:10.2307/3431091 PMID:2272326
- Roggli VL (2004). *Asbestos bodies and nonasbestos ferruginous bodies*. In: *Pathology of Asbestos-Associated Diseases*. Roggli VL, editor. New York: Springer, pp. 34–70.
- Roggli VL (2006). The role of analytical SEM in the determination of causation in malignant mesothelioma. *Ultrastruct Pathol*, 30: 31–35. doi:10.1080/01913120500313192 PMID:16517468
- Roggli VL, Greenberg SD, McLarty JL *et al.* (1980). Asbestos body content of the larynx in asbestos workers. A study of five cases. *Arch Otolaryngol*, 106: 533–535. PMID:7406758
- Rohl AN, Langer AM, Selikoff IJ *et al.* (1976). Consumer talcums and powders: mineral and chemical characterization. *J Toxicol Environ Health*, 2: 255–284. doi:10.1080/15287397609529432 PMID:1011287
- Roller M, Pott F, Kamino K *et al.* (1996). Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres. *Exp Toxicol Pathol*, 48: 3–12. PMID:8919265
- Roskill Information Services Ltd (2003). *The Economics of Talc 7 Pyrophyllite*, 9th Ed. London, pp. 102–110.
- Rösler JA, Woitowitz HJ, Lange HJ *et al.* (1994). Mortality rates in a female cohort following asbestos exposure in Germany. *J Occup Med*, 36: 889–893. PMID:7807270
- Rowlands N, Gibbs GW, McDonald AD (1982). Asbestos fibres in the lungs of chrysotile miners and millers—a preliminary report. *Ann Occup Hyg*, 26: 411–415. doi:10.1093/annhyg/26.3.411 PMID:6295244
- Rubino GF, Scansetti G, Piolatto G, Romano CA (1976). Mortality study of talc miners and millers. *J Occup Med*, 18: 186–193. PMID:1255280 doi:10.1097/00043764-197603000-00013
- Ruda TA & Dutta PK (2005). Fenton chemistry of Fe(III)-exchanged zeolitic minerals treated with antioxidants. *Environ Sci Technol*, 39: 6147–6152. doi:10.1021/es050336e PMID:16173575
- Saalo A, Lämsimäki E, Heikkilä M, Kauppinen T (2006). ASA 2006. Syöpäsairauden vaaraa aiheuttaville aineille ja menetelmille ammatissaan altistuneiksi ilmoitetut Suomessa. (In Finnish)
- Sanchez VC, Pietruska JR, Miselis NR *et al.* (2009). Biopersistence and potential adverse health impacts of fibrous nanomaterials: what have we learned from asbestos? *Wiley Interdiscip Rev Nanomed Nanobiotechnol*, 1: 511–529. PMID:20049814
- Sato M, Shames DS, Gazdar AF, Minna JD (2007). A translational view of the molecular pathogenesis of lung cancer. *J Thorac Oncol*, 2: 327–343. doi:10.1097/01.JTO.0000263718.69320.4c PMID:17409807
- Schwartz AG, Prysak GM, Bock CH, Cote ML (2007). The molecular epidemiology of lung cancer. *Carcinogenesis*, 28: 507–518. doi:10.1093/carcin/bgl253 PMID:17183062
- Sébastien P, Awad L, Bignon J *et al.* (1984). Ferruginous bodies in sputum as an indication of exposure to airborne mineral fibres in the mesothelioma villages of Cappadocia. *Arch Environ Health*, 39: 18–23. PMID:6324702
- Seidman H, Selikoff IJ, Gelb SK (1986). Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am J Ind Med*, 10: 479–514. PMID:2880502
- Sekido Y, Fong KM, Minna JD (2001). *Cancer of the lung*. In: *Cancer: Principles & Practice of Oncology*, 6th ed. Devita VT, Jr., Hellman S, Rosenbert SA, editors. Philadelphia: Lippincoll Williams & Wilkins
- Selikoff IJ, Bader RA, Bader ME *et al.* (1967). Asbestosis and neoplasia. *Am J Med*, 42: 487–496. doi:10.1016/0002-9343(67)90049-6 PMID:5336987
- Selikoff IJ, Churg J, Hammond EC (1964). Asbestos exposure and neoplasia. *JAMA*, 188: 22–26. PMID:14107207
- Selikoff IJ & Hammond EC (1979). Asbestos and smoking. *JAMA*, 242: 458–459. doi:10.1001/jama.242.5.458 PMID:448967
- Selikoff IJ, Hammond EC, Seidman H (1979). Mortality experience of insulation workers in the United States

- and Canada, 1943--1976. *Ann N Y Acad Sci*, 330: 1 Health Hazard91-116. doi:10.1111/j.1749-6632.1979.tb18711.x PMID:294225
- Selikoff IJ & Seidman H (1991). Asbestos-associated deaths among insulation workers in the United States and Canada, 1967-1987. *Ann N Y Acad Sci*, 643: 1 The Third Wave1-14. doi:10.1111/j.1749-6632.1991.tb24439.x PMID:1809121
- Shah KV (2004). Simian virus 40 and human disease. *J Infect Dis*, 190: 2061-2064. doi:10.1086/425999 PMID:15551202
- Shukla A, Gulumian M, Hei TK *et al.* (2003). Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. *Free Radic Biol Med*, 34: 1117-1129. doi:10.1016/S0891-5849(03)00060-1 PMID:12706492
- Sluis-Cremer GK, Liddell FD, Logan WP, Bezuidenhout BN (1992). The mortality of amphibole miners in South Africa, 1946-80. *Br J Ind Med*, 49: 566-575. PMID:1325180
- Smailyte G, Kurtinaitis J, Andersen A (2004). Cancer mortality and morbidity among Lithuanian asbestos-cement producing workers. *Scand J Work Environ Health*, 30: 64-70. PMID:15018030
- Smith DM, Ortiz LW, Archuleta RF, Johnson NF (1987). Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres. *Ann Occup Hyg*, 31: 4B731-754. doi:10.1093/annhyg/31.4B.731 PMID:2835925
- Stanton MF, Layard M, Tegeris A *et al.* (1981). Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *J Natl Cancer Inst*, 67: 965-975. PMID:6946253
- Stayner L, Kuempel E, Gilbert S *et al.* (2008). An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. *Occup Environ Med*, 65: 613-619. doi:10.1136/oem.2007.035584 PMID:18096653
- Stayner LT, Dankovic DA, Lemen RA (1996). Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. *Am J Public Health*, 86: 179-186. doi:10.2105/AJPH.86.2.179 PMID:8633733
- Sullivan PA (2007). Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. *Environ Health Perspect*, 115: 579-585. doi:10.1289/ehp.9481 PMID:17450227
- Suzuki Y & Yuen SR (2001). Asbestos tissue burden study on human malignant mesothelioma. *Ind Health*, 39: 150-160. doi:10.2486/indhealth.39.150 PMID:11341545
- Suzuki Y, Yuen SR, Ashley R (2005). Short, thin asbestos fibres contribute to the development of human malignant mesothelioma: pathological evidence. *Int J Hyg Environ Health*, 208: 201-210. doi:10.1016/j.ijheh.2005.01.015 PMID:15971859
- Szeszenia-Dabrowska N, Urszula W, Szymczak W, Strzelecka A (2002). Mortality study of workers compensated for asbestosis in Poland, 1970-1997. *Int J Occup Med Environ Health*, 15: 267-278. PMID:12462454
- Szeszenia-Dabrowska N, Wilczyńska U, Szymczak W, Laskowicz K (1998). Environmental exposure to asbestos in asbestos cement workers: a case of additional exposure from indiscriminate use of industrial wastes. *Int J Occup Med Environ Health*, 11: 171-177. PMID:9753896
- Tomatis M, Prandi L, Bodoardo S, Fubini B (2002). Loss of surface reactivity upon heating amphibole asbestos. *Langmuir*, 18: 4345-4350. doi:10.1021/la011609w
- Toyooka S, Pass HI, Shivapurkar N *et al.* (2001). Aberrant methylation and simian virus 40 tag sequences in malignant mesothelioma. *Cancer Res*, 61: 5727-5730. PMID:11479207
- Tsou JA, Galler JS, Wali A *et al.* (2007). DNA methylation profile of 28 potential marker loci in malignant mesothelioma. *Lung Cancer*, 58: 220-230. doi:10.1016/j.lungcan.2007.06.015 PMID:17659810
- Tsou JA, Shen LY, Siegmund KD *et al.* (2005). Distinct DNA methylation profiles in malignant mesothelioma, lung adenocarcinoma, and non-tumor lung. *Lung Cancer*, 47: 193-204. doi:10.1016/j.lungcan.2004.08.003 PMID:15639718
- Tulchinsky TH, Ginsberg GM, Iscovich J *et al.* (1999). Cancer in ex-asbestos cement workers in Israel, 1953-1992. *Am J Ind Med*, 35: 1-8. doi:10.1002/(SICI)1097-0274(199901)35:1<1::AID-AJIM1>3.0.CO;2-5 PMID:9884739
- Turci F, Favero-Longo SE, Tomatis M *et al.* (2007). A biomimetic approach to the chemical inactivation of chrysotile fibres by lichen metabolites. *Chemistry*, 13: 4081-4093. doi:10.1002/chem.200600991 PMID:17295378
- Turci F, Tomatis M, Compagnoni R *et al.* (2009). Role of associated mineral fibres in chrysotile asbestos health effects: the case of balangeroite. *Ann Occup Hyg*, 53: 491-497. PMID:19435981.
- Ugolini D, Neri M, Ceppi M *et al.* (2008). Genetic susceptibility to malignant mesothelioma and exposure to asbestos: the influence of the familial factor. *Mutat Res*, 658: 162-171. doi:10.1016/j.mrrev.2007.08.001 PMID:17904414
- Upadhyay D & Kamp DW (2003). Asbestos-induced pulmonary toxicity: role of DNA damage and apoptosis. *Exp Biol Med (Maywood)*, 228: 650-659. PMID:12773695
- US EPA (2010). Toxics Release Inventory, Chemical Reports. (<http://www.epa.gov/triexplorer/>)
- USGS (2001). Some Facts about Asbestos (USGS Fact Sheet FS-012-01), 4 pp.
- Vainio H & Boffetta P (1994). Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. *Scand J Work Environ Health*, 20: 235-242. PMID:7801068

IARC MONOGRAPHS – 100C

- Valinluck V & Sowers LC (2007). Endogenous cytosine damage products alter the site selectivity of human DNA maintenance methyltransferase DNMT1. *Cancer Res*, 67: 946–950. doi:10.1158/0008-5472.CAN-06-3123 PMID:17283125
- Van Gosen BS (2006) Reported historic asbestos mines, historic asbestos prospects, and natural asbestos occurrences in the Eastern United States: U.S. Geological Survey Open-File Report 2005–1189. Available at <http://pubs.usgs.gov/of/2005/1189/>
- Van Gosen BS, Lowers HA, Sutley SJ, Gent CA (2004). Using the geologic setting of talc deposits as an indicator of amphibole asbestos content. *Environ Geol*, 45: 920–939. doi:10.1007/s00254-003-0955-2
- Vasama-Neuvonen K, Pukkala E, Paakkulainen H *et al.* (1999). Ovarian cancer and occupational exposures in Finland. *Am J Ind Med*, 36: 83–89. doi:10.1002/(SICI)1097-0274(199907)36:1<83::AID-AJIM12>3.0.CO;2-Q PMID:10361591
- Vineis P, Ciccone G, Magnino A (1993). Asbestos exposure, physical activity and colon cancer: a case-control study. *Tumori*, 79: 301–303. PMID:8116070
- Virta RL (2002). *Asbestos: Geology, Mineralogy, Mining, and Uses (Open-File Report 02–149)*. Reston, VA: US Geological Survey, pp. 28 [<http://pubs.usgs.gov/of/2002/of02-149/of02-149.pdf>]
- Virta RL (2006). *Worldwide asbestos supply and consumption trends from 1900 through 2003*. Reston, VA: US Geological Survey, Circular 1298.
- Virta RL (2008). *2007 Minerals Yearbook – Asbestos [Advance Release]*. Reston, VA: US Geological Survey, pp. 7
- Virta RL (2009). *Mineral Commodity Summaries: Talc and Pyrophyllite*. Reston, VA: US Geological Surveys, pp. 162–163.
- Wagner JC (1962). Experimental production of mesothelial tumours of the pleura by implantation of dusts in laboratory animals. *Nature*, 196: 180–181. doi:10.1038/196180a0 PMID:13998252
- Wagner JC (1990). *Biological effects of short fibres*. In: *Proceedings of the VIIth International Pneumoconiosis Conference, Pittsburgh, Pennsylvania, USA, August 23–26 1988. DHHS NIOSH Publ. No. 90–108 Part II*. Washington, D.C.: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, pp. 835–839.
- Wagner JC & Berry G (1969). Mesotheliomas in rats following inoculation with asbestos. *Br J Cancer*, 23: 567–581. PMID:5360333
- Wagner JC, Berry G, Hill DE *et al.* (1984b). *Animal experiments with MMMVF effects of inhalation and intrapleural inoculation in rats*. In: *Biological Effects of Man-made Mineral Fibres: Proceedings of a WHO/IARC conference in association with JEMRB and TIMA. Copenhagen, April 20–22, 1982*. Copenhagen: Regional Office for Europe World Health Organization, pp. 209–233.
- Wagner JC, Berry G, Skidmore JW, Pooley FD (1980). The comparative effects of three chrysotiles by injection and inhalation in rats. *IARC Sci Publ*, 30: 363–372. PMID:7239658
- Wagner JC, Berry G, Skidmore JW, Timbrell V (1974). The effects of the inhalation of asbestos in rats. *Br J Cancer*, 29: 252–269. PMID:4364384
- Wagner JC, Berry G, Timbrell V (1973). Mesotheliomata in rats after inoculation with asbestos and other materials. *Br J Cancer*, 28: 173–185. PMID:4354178
- Wagner JC, Griffiths DM, Hill RJ (1984a). The effect of fibre size on the in vivo activity of UICC crocidolite. *Br J Cancer*, 49: 453–458. PMID:6324841
- Wagner JC, Griffiths DM, Munday DE (1987). Experimental studies with palygorskite dusts. *Br J Ind Med*, 44: 749–763. PMID:2961365
- Wagner JC & Pooley FD (1986). Mineral fibres and mesothelioma. *Thorax*, 41: 161–166. doi:10.1136/thx.41.3.161 PMID:3715773
- Wagner JC, Skidmore JW, Hill RJ, Griffiths DM (1985). Erionite exposure and mesotheliomas in rats. *Br J Cancer*, 51: 727–730. PMID:2986668
- Wagner JC, Sleggs CA, Marchand P (1960). Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med*, 17: 260–271. PMID:13782506
- Wali A, Morin PJ, Hough CD *et al.* (2005). Identification of intelectin overexpression in malignant pleural mesothelioma by serial analysis of gene expression (SAGE). *Lung Cancer*, 48: 19–29. doi:10.1016/j.lungcan.2004.10.011 PMID:15777968
- Walser T, Cui X, Yanagawa J *et al.* (2008). Smoking and lung cancer: the role of inflammation. *Proc Am Thorac Soc*, 5: 811–815. doi:10.1513/pats.200809-100TH PMID:19017734
- Ward JM, Frank AL, Wenk M *et al.* (1980). Ingested asbestos and intestinal carcinogenesis in F344 rats. *J Environ Pathol Toxicol*, 3: 301–312. PMID:7441086
- Webster I, Goldstein B, Coetzee FS, van Sittert GCH (1993). Malignant mesothelioma induced in baboons by inhalation of amosite asbestos. *Am J Ind Med*, 24: 659–666. doi:10.1002/ajim.4700240602 PMID:8311096
- Weiner R, Rees D, Lunga FJP, Felix MA (1994). Third wave of asbestos-related disease from secondary use of asbestos. A case report from industry. *S Afr Med J*, 84: 158–160. PMID:7740353
- Weiner SJ & Neragi-Miandoab S (2009). Pathogenesis of malignant pleural mesothelioma and the role of environmental and genetic factors. *J Cancer Res Clin Oncol*, 135: 15–27. doi:10.1007/s00432-008-0444-9 PMID:18787841
- Welch LS, Acherman YI, Haile E *et al.* (2005). Asbestos and peritoneal mesothelioma among college-educated

- men. *Int J Occup Environ Health*, 11: 254–258. PMID:16130966
- WHO (2006). Elimination of Asbestos Related Diseases. WHO/SDE/OEH/06.03. Geneva: World Health Organization.
- Wigle DT (1977). Cancer mortality in relation to asbestos in municipal water supplies. *Arch Environ Health*, 32: 185–190. PMID:889357
- Wignall BK & Fox AJ (1982). Mortality of female gas mask assemblers. *Br J Ind Med*, 39: 34–38. PMID:7066218
- Williams P, Paustenbach D, Balzer JL, Mangold C (2007a). Retrospective exposure assessment of airborne asbestos related to skilled craftsmen at a petroleum refinery in Beaumont, Texas (1940–2006). *J Toxicol Environ Health A*, 70: 1076–1107. doi:10.1080/15287390701208305 PMID:17558804
- Williams PRD, Phelka AD, Paustenbach DJ (2007b). A review of historical exposures to asbestos among skilled craftsmen (1940–2006). *J Toxicol Environ Health Part B*, 10: 319–377. PMID:17687724.
- Wypych F, Adad LB, Mattoso N *et al.* (2005). Synthesis and characterization of disordered layered silica obtained by selective leaching of octahedral sheets from chrysotile and phlogopite structures. *J Colloid Interface Sci*, 283: 107–112. doi:10.1016/j.jcis.2004.08.139 PMID:15694430
- Yu HB & Finlay BB (2008). The caspase-1 inflammatory: a pilot of innate immune responses. *Cell Host Microbe*, 4: 198–208. doi:10.1016/j.chom.2008.08.007 PMID:18779046
- Zazenski R, Ashton WH, Briggs D *et al.* (1995). Talc: occurrence, characterization, and consumer applications. *Regul Toxicol Pharmacol*, 21: 218–229. doi:10.1006/rtph.1995.1032 PMID:7644709
- Zhang YL & Wang PL (1984). Gastric cancer associated with incomplete pyloric obstruction and belching combustible gas. *Chin Med J (Engl)*, 97: 66 PMID:6428835
- Zheng W, Blot WJ, Shu XO *et al.* (1992). Risk factors for oral and pharyngeal cancer in Shanghai, with emphasis on diet. *Cancer Epidemiol Biomarkers Prev*, 1: 441–448. PMID:1302555
- Zhu H & Wang Z (1993). Study of occupational lung cancer in asbestos factories in China. *Br J Ind Med*, 50: 1039–1042. PMID:8280629

SILICA DUST, CRYSTALLINE, IN THE FORM OF QUARTZ OR CRISTOBALITE

Silica was considered by previous IARC Working Groups in 1986, 1987, and 1996 ([IARC, 1987a, b, 1997](#)). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Silica, or silicon dioxide (SiO_2), is a group IV metal oxide, which naturally occurs in both crystalline and amorphous forms (i.e. polymorphic; [NTP, 2005](#)). The various forms of crystalline silica are: α -quartz, β -quartz, α -tridymite, β -tridymite, α -cristobalite, β -cristobalite, keatite, coesite, stishovite, and moganite ([NIOSH, 2002](#)). The most abundant form of silica is α -quartz, and the term quartz is often used in place of the general term crystalline silica ([NIOSH, 2002](#)).

1.1 Identification of the agent

α -Quartz is the thermodynamically stable form of crystalline silica in ambient conditions. The overwhelming majority of natural crystalline silica exists as α -quartz. The other forms exist in a metastable state. The nomenclature used is that of α for a lower-temperature phase, and β for a higher-temperature phase. Other notations exist and the prefixes low- and high- are also used ([IARC, 1997](#)). The classification and nomenclature of silica forms are summarized in [Table 1.1](#). For more detailed information, refer to the previous *IARC Monograph* ([IARC, 1997](#)).

1.2 Chemical and physical properties of the agent

Selected chemical and physical properties of silica and certain crystalline polymorphs are summarized in [Table 1.1](#). For a detailed discussion of the crystalline structure and morphology of silica particulates, and corresponding physical properties and domains of thermodynamic stability, refer to the previous *IARC Monograph* ([IARC, 1997](#)).

1.3 Use of the agent

The physical and chemical properties of silica make it suitable for many uses. Most silica in commercial use is obtained from naturally occurring sources, and is categorized by end-use or industry ([IARC, 1997](#); [NTP, 2005](#)). The three predominant commercial silica product categories are: sand and gravel, quartz crystals, and diatomites.

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Table 1.1 Nomenclature, CAS numbers, and classification of silica forms with selected physical and chemical properties

Name	CAS No.	Basic Formula	Classification	Synonyms	Properties
Silica	7631-86-9	SiO ₂	α-quartz, β-quartz; α-tridymite, β1-tridymite, β2-tridymite; α-cristobalite, β-cristobalite; coesite; stishovite; moganite		<u>Structure</u> : crystalline, amorphous, cryptocrystalline <u>Molecular weight</u> : 60.1 <u>Solubility</u> : poorly soluble in water at 20 °C and most acids; increases with temperature and pH <u>Reactivity</u> : reacts with alkaline aqueous solutions, with hydrofluoric acid (to produce silicon tetrafluoride gas), and catechol
Crystalline Silica					
Cristobalite	14464-46-1		α-cristobalite, β-cristobalite		
Quartz	14808-60-7		α-quartz, β-quartz	α-quartz: agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli	<u>Solubility</u> : 6–11 µg/cm ³ (6–11 ppm) at room temperature; slightly soluble in body fluids <u>Thermodynamic properties</u> : melts to a glass; coefficient of expansion by heat—lowest of any known substance
Tripoli	1317-95-9				
Tridymite	15468-32-3		α-tridymite, β1-tridymite, β2-tridymite		

From [IARC \(1997\)](#), [NIOSH \(2002\)](#), [NTP \(2005\)](#)

1.3.1 Sand and gravel

Although silica sand has been used for many different purposes throughout history, its most ancient and principal use has been in the manufacture of glass (e.g. containers, flat plate and window, and fibreglass). Sands are used in ceramics (e.g. pottery, brick, and tile), foundry (e.g. moulding and core, refractory), abrasive (e.g. blasting, scouring cleansers, sawing and sanding), hydraulic fracturing applications, and many other uses. Several uses require the material to be ground (e.g. scouring cleansers, some types of fibreglass, certain foundry applications). In some uses (e.g. sandblasting, abrasives), grinding

also occurs during use. For a more complete list of end-uses, refer to Table 8 of the previous *IARC Monograph* ([IARC, 1997](#)).

According to the US Geological Survey, world production in 2008 was estimated to be 121 million metric tons ([Dolley, 2009](#)). The leading producers were the USA (30.4 million metric tons), Italy (13.8 million metric tons), Germany (8.2 million metric tons), the United Kingdom (5.6 million metric tons), Australia (5.3 million metric tons), France (5 million metric tons), Spain (5 million metric tons), and Japan (4.5 million metric tons).

1.3.2 Quartz crystals

Quartz has been used for several thousand years in jewellery as a gem stone (e.g. amethyst, citrine), and is used extensively in both the electronics and optical components industries. Electronic-grade quartz is used in electronic circuits, and optical-grade quartz is used in windows, and other specialized devices (e.g. lasers) ([IARC, 1997](#)).

1.3.3 Diatomites

Diatomites are used in filtration, as fillers (in paint, paper, synthetic rubber goods, laboratory absorbents, anti-caking agents, and scouring powders), and as carriers for pesticides. They impart abrasiveness to polishes, flow and colour qualities to paints, and reinforcement to paper. Other uses include: insulators, absorption agents, scourer in polishes and cleaners, catalyst supports, and packing material ([IARC, 1997](#)).

According to the US Geological Survey, world production in 2008 was estimated to be 2.2 million metric tons. The USA accounted for 35% of total world production, followed by the People's Republic of China (20%), Denmark (11%), Japan (5%), Mexico (4%), and France (3%) ([Crangle, 2009](#)).

1.4 Environmental occurrence

Keatite, coesite, stishovite, and moganite are rarely found in nature. The most commonly occurring polymorphs are quartz, cristobalite and tridymite, which are found in rocks and soil. These forms of silica can be released to the environment via both natural and anthropogenic sources (e.g. foundry processes, brick and ceramics manufacturing, silicon carbide production, burning of agricultural waste or products, or calcining of diatomaceous earth). Some of these anthropogenic activities may cause transformation of one polymorph into another ([NIOSH, 2002](#)).

1.4.1 Natural occurrence

α -Quartz is found in trace to major amounts in most rock types (e.g. igneous, sedimentary, metamorphic, argillaceous), sands, and soils. The average quartz composition of major igneous and sedimentary rocks is summarized in Table 10 of the previous *IARC Monograph* ([IARC, 1997](#)). Quartz is a major component of soils, composing 90–95% of all sand and silt fractions in a soil. It is the primary matrix mineral in the metalliferous veins of ore deposits, and can also be found in semiprecious stones, such as amethyst, citrine, smoky quartz, morion, and tiger's eye ([IARC, 1997](#)).

Crystalline tridymite and cristobalite are found in acid volcanic rocks. Cristobalite also occurs in some bentonite clays, and as traces in diatomite. Although rarely found in nature, coesite and stishovite have been found in rocks that equilibrated in short-lived high-pressure environments (e.g. meteoritic impact craters), and keatite has been found in high-altitude atmospheric dusts, which are believed to originate from volcanic sources ([IARC, 1997](#)).

For a more detailed description of the natural occurrence of crystalline silica and its polymorphs in air, water and soil, refer to the previous *IARC Monograph* ([IARC, 1997](#)).

1.5 Human exposure

1.5.1 Exposure of the general population

Inhalation of crystalline silica during the use of commercial products containing quartz is thought to be the primary route of exposure for the non-occupationally exposed (i.e. general) population. Commercial products containing quartz include: cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, putty, paint, and mortar. No quantitative data on potential levels of exposure during the use of these products were available at the time of

writing ([WHO, 2000](#)). The general population may also be exposed via ingestion of potable water containing quartz particles; however, quantitative data on concentrations of quartz in potable or other forms of drinking-water were again not available ([IARC, 1997](#); [WHO, 2000](#)).

1.5.2 Occupational exposure

Because of the extensive natural occurrence of crystalline silica in the earth's crust and the wide uses of the materials in which it is a constituent, workers may be exposed to crystalline silica in a large variety of industries and occupations ([IARC, 1997](#)). [Table 1.2](#) lists the main industries and activities in which workers could be exposed to crystalline silica. Included in this table are activities that involve the movement of earth (e.g. mining, farming, construction, quarrying), disturbance of silica-containing products (e.g. demolition of masonry and concrete), handling or use of sand- and other silica-containing products (e.g. foundry processes, such as casting, furnace installation and repair; abrasive blasting; production of glass, ceramics, abrasives, cement, etc.).

Estimates of the number of workers potentially exposed to respirable crystalline silica have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupational Exposure Survey (NOES), conducted during 1981–83, and the *County Business Patterns 1986*, NIOSH estimated that about 1.7 million US workers were potentially exposed to respirable crystalline silica ([NIOSH, 2002](#)). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that more than 3.2 million workers in the then 15 Member States of the European Union during 1990–93 were considered as occupationally exposed to respirable crystalline silica above background

level ([Kauppinen et al., 2000](#)). Nearly 87% of these workers were employed in 'construction' ($n = 2080000$), 'manufacture of other non-metallic mineral products' ($n = 191000$), 'other mining' ($n = 132000$), 'manufacture of pottery, china and earthenware' ($n = 96000$), 'manufacture of machinery except electrical' ($n = 78000$), 'iron and steel basic industries' ($n = 68000$), 'manufacture of fabricated metal products, except machinery and equipment' ($n = 68000$), and 'metal ore mining' ($n = 55000$). The countries with the highest number of potentially exposed workers were: Germany (1 million workers), the United Kingdom (580000 workers), Spain (400000 workers), Italy (250000 workers), the Netherlands (170000 workers), France (110000 workers), and Austria (100000 workers) ([Kauppinen et al., 2000](#); [Mirabelli & Kauppinen, 2005](#); [Scarselli et al., 2008](#)).

For representative data in the main industries where quantitative exposure levels were available in the published literature and/or where major occupational health studies had been conducted, refer to the previous *IARC Monograph* ([IARC, 1997](#)). These main industries include mines and quarries, foundries and other metallurgical operations, ceramics and related industries, construction, granite, crushed stone and related industries, sandblasting of metal surfaces, agriculture, and miscellaneous other operations ([IARC, 1997](#)). Data from studies and reviews on crystalline silica exposure published since the previous *IARC Monograph* are summarized below.

(a) Levels of occupational exposure

To estimate the number of US workers potentially exposed to high levels of crystalline silica and to examine trends in exposure over time, [Yassin et al. \(2005\)](#) analysed data contained in the OSHA Integrated Management Information System (IMIS) database. After exclusion of duplicate bulk and area samples, a total of 7209 personal sample measurements collected during

Silica dust, crystalline (quartz or cristobalite)

Table 1.2 Main activities in which workers may be exposed to crystalline silica

Industry/activity	Specific operation/task	Source material
Agriculture	Ploughing, harvesting, use of machinery	Soil
Mining and related milling operations	Most occupations (underground, surface, mill) and mines (metal and non-metal, coal)	Ores and associated rock
Quarrying and related milling operations	Crushing stone, sand and gravel processing, monumental stone cutting and abrasive blasting, slate work, diatomite calcination	Sandstone, granite, flint, sand, gravel, slate, diatomaceous earth
Construction	Abrasive blasting of structures, buildings Highway and tunnel construction Excavation and earth-moving Masonry, concrete work, demolition	Sand, concrete Rock Soil and rock Concrete, mortar, plaster
Glass, including fibreglass	Raw material processing Refractory installation and repair	Sand, crushed quartz Refractory materials
Cement	Raw materials processing	Clay, sand, limestone, diatomaceous earth
Abrasives	Silicon carbide production Abrasive products fabrication	Sand Tripoli, sandstone
Ceramics, including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels	Mixing, moulding, glaze or enamel spraying, finishing	Clay, shale, flint, sand, quartzite, diatomaceous earth
Iron and steel mills	Refractory preparation and furnace repair	Refractory material
Silicon and ferro-silicon	Raw materials handling	Sand
Foundries (ferrous and non-ferrous)	Casting, shaking out Abrasive blasting, fettling Furnace installation and repair	Sand Sand Refractory material
Metal products including structural metal, machinery, transportation equipment	Abrasive blasting	Sand
Shipbuilding and repair	Abrasive blasting	Sand
Rubber and plastics	Raw material handling	Fillers (tripoli, diatomaceous earth)
Paint	Raw materials handling	Fillers (tripoli, diatomaceous earth, silica flour)
Soaps and cosmetics	Abrasive soaps, scouring powders	Silica flour
Asphalt and roofing felt	Filling and granule application	Sand and aggregate, diatomaceous earth
Agricultural chemicals	Raw material crushing, handling	Phosphate ores and rock
Jewellery	Cutting, grinding, polishing, buffing	Semiprecious gems or stones, abrasives
Dental material	Sandblasting, polishing	Sand, abrasives
Automobile repair	Abrasive blasting	Sand
Boiler scaling	Coal-fired boilers	Ash and concretions

From [IARC, 1997](#)

2512 OSHA inspections during 1988–2003 were analysed. The findings suggest that geometric mean crystalline silica exposure levels declined in some high-risk construction industries during the period under study, and revealed a significant

decline when compared with silica exposure levels found in a previous study by [Stewart & Rice \(1990\)](#). Geometric mean airborne silica exposure levels among workers in the following industries were significantly lower in 1988–2003

than in 1979–87: general contractor industry (0.057 mg/m³ versus 0.354 mg/m³), bridge-tunnel construction industry (0.069 mg/m³ versus 0.383 mg/m³), and stonework masonry industry (0.065 mg/m³ versus 0.619 mg/m³). Silica exposures in the grey-iron industry also declined by up to 54% for some occupations (e.g. the geometric mean for “furnace operators” in 1979–87 was 0.142 mg/m³ versus 0.066 mg/m³ in 1988–2003). [The Working Group noted that exposure levels may not have decreased globally.]

[Table 1.3](#) presents the more recent studies that assessed the levels of respirable crystalline silica in a range of industries and countries. Other recent exposure studies that did not measure the respirable crystalline silica components are presented below.

(b) Mines

As part of a cohort mortality study follow-up in four tin mines in China, [Chen et al. \(2006\)](#) developed quantitative exposure estimates of silica mixed dust. Workers in the original cohort were followed up from the beginning of 1972 to the end of 1994. Cumulative exposure estimates were calculated for each worker using their mine employment records and industrial hygiene measurements of airborne total dust, particle size, and free silica content collected since the 1950s. Total dust concentrations of the main job titles exposed were found to have declined from about 10–25 mg/m³ in the beginning of the 1950s to about 1–4 mg/m³ in the 1980s and 1990s. The respirable fraction of total dust was estimated to be 25 ± 4%, and the respirable crystalline silica concentration was estimated to be 4.3% of the total mixed mine dust

[Tse et al. \(2007\)](#) conducted a cross-sectional study to investigate the prevalence of accelerated silicosis among 574 gold miners in Jiangxi, China. Using occupational hygiene data abstracted from government documents and bulk dust data from a study in another gold mine in the region, the estimated mean concentration of respirable

silica dust were reported as 89.5 mg/m³ (range, 70.2–108.8 mg/m³). According to government documents, the total dust concentration in underground gold mining was in the range of 102.6–159 mg/m³ (average, 130.8 mg/m³), and the fraction of silica in total dust was around 75.7–76.1%. No data on the proportion of respirable dust were available.

To determine dose–response relationships between exposure to respirable dust and respiratory health outcomes, [Naidoo et al. \(2006\)](#) used historical data ($n = 3645$) and current measurements ($n = 441$) to characterize exposure to respirable coal mine dust in three South African coal mines. Jobs were classified into the following exposure zones: face (directly involved with coal extraction), underground backbye (away from the coal mining face), and work on the surface. Based on the 8-hour full-shift samples collected respectively, mean respirable dust concentrations in Mines 1, 2, and 3, were as follows: 0.91 mg/m³ (GSD, 3.39; mean silica content, 2.3%; $n = 102$), 1.28 mg/m³ (GSD, 2.11; mean silica content, 1.4%; $n = 63$), and 1.90 mg/m³ (GSD, 2.23; mean silica content, 2.7%; $n = 73$) at the face; 0.48 mg/m³ (GSD, 2.97; mean silica content, 1.48%; $n = 30$), 0.56 mg/m³ (GSD, 3.71; mean silica content, 1.35%; $n = 47$), and 0.52 mg/m³ (GSD, 4.06; mean silica content, 0.9%; $n = 41$) in the backbye zone; and, 0.31 mg/m³ (GSD, 3.52; mean silica content, 0.95%; $n = 8$), 0.15 mg/m³ (GSD, 3.56; $n = 6$), and 0.24 mg/m³ (GSD, 7.69; mean silica content, 0.64%; $n = 11$) in the surface zone. Based on the historical data, overall geometric mean dust levels were 0.9 mg/m³ (GSD, 4.9), 1.3 mg/m³ (GSD, 3.3), and 0.5 mg/m³ (GSD, 5.6) for Mines 1, 2, and 3, respectively.

(c) Granite-quarrying and -processing, crushed stone, and related industries

[Bahrami et al. \(2008\)](#) described the personal exposure to respirable dust and respirable quartz in stone-crushing units located in western Islamic Republic of Iran. A total of 40 personal samples

Silica dust, crystalline (quartz or cristobalite)

Table 1.3 Respirable crystalline silica concentrations in various industries worldwide

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m ³)	Number of samples	Comments
Mines				
Hayumbu et al. (2008) , copper mines, the Zambia		<u>Arithmetic mean</u> (SD; range)		Cross-sectional dust exposure assessment; bulk and personal respirable samples; NIOSH method 0600 for gravimetric analysis of respirable dust; NIOSH method 7500 for quartz analysis of bulk and respirable samples; mean personal sampling time: 307 minutes (Mine 1) and 312 minutes (Mine 2)
	Mine 1	0.14 (0.2; 0–1.3)	101	
	Mine 2	0.06 (0.06; 0–0.3)	102	
Weeks & Rose (2006) , metal and non-metal mines, USA, 1998–2002		<u>Arithmetic mean</u> (GM)		Mine Safety and Health Administration compliance data from 4726 mines; 8-hour full-shift personal air samples; gravimetric analysis of respirable dust; NIOSH method 7500 for silica analysis; arithmetic and geometric mean exposure calculated and classified by occupation, mine, and state
	Strip and open pit mines	0.047 (0.027)	13702	
	Mills or preparation plants	0.045 (0.027)	1145	
	Underground mines	0.050 (0.029)	1360	
	Overall	0.047 (0.027)	16207	
Brätveit et al. (2003) underground small-scale mining, United Republic of Tanzania, 2001		<u>Geometric mean</u> (GSD)		Personal dust sampling (respirable and total dust) on 3 consecutive day shifts; sampling time varied between 5 and 8 hours; gravimetric analysis of respirable and total dust; NIOSH method 7500 for silica analysis
	Drilling, blasting, and shovelling	2.0 (1.7)	6	
	Shovelling and loading of sacks	1.0 (1.5)	3	
	Overall	1.6 (1.8)	9	
Park et al. (2002) diatomaceous earth mining and milling, California, USA, 1942–94	Mines and mills	<u>Arithmetic mean</u> 0.29 Cumulative exposure (mg/m ³ -yr) 2.16	NR	Re-analysis of data from a cohort of 2342 California diatomaceous earth workers; mean concentration of respirable crystalline silica averaged over years of employment of cohort; crystalline silica content of bulk samples varied from 1–25%, and depended on process location
		<u>Geometric mean</u> (GSD)		Personal dust samples collected during two periods in 2003 and 2004; 134 respirable dust samples collected and analysed gravimetrically; 125 samples analysed for quartz using NIOSH method 7500
	Development team	0.073 (11.1)	56	
Mamuya et al. (2006) underground coal mining, United Republic of Tanzania; June–August 2003 and July–August 2004	Mine team	0.013 (2.97)	45	
	Transport team	0.006 (1.84)	11	
	Maintenance team	0.016 (11.05)	13	
	Overall	0.027 (8.18)	125	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m ³)	Number of samples	Comments
Granite-quarrying and -processing, crushed stone, and related industries				
Wickman & Middendorf (2002)		Arithmetic mean (SD)		Exposure assessment surveys in 10 granite sheds to measure compliance; full-shift respirable dust samples in workers' breathing zone and area samples; gravimetric analysis of respirable dust; crystalline silica analysis using OSHA ID 142; TWA exposures calculated
Granite-quarrying, Georgia, USA; May 1993–February 1994	Granite sheds	0.052 (0.047)	40	
Brown & Rushton (2005a)		Unadjusted geometric mean (GSD)		Samples collected by companies as part of routine monitoring programme; gravimetric analysis; silica content measured by Fourier transform infrared spectrophotometry until 1997 and by X-ray diffraction thereafter; personal and static measurements combined into one data set
Industrial silica sand, United Kingdom, 1978–2000	Quarries	0.09 (3.9)	2429 (personal) 583 (static)	
Gottesfeld et al. (2008)		Arithmetic mean (SD)		Bulk and personal air samples collected; silica analysis using NIOSH method 7500; NIOSH method 0500 for respirable particulates used in 2003
Stone-crushing mills, India, 2003 (initial phase), 2006 and 2007 (post-implementation of engineering controls)	Prior to water-spray controls (2003)	Cristobalite, 0.09 (0.08) Quartz, 0.25 (0.12)	[5] [5]	
	After water-spray controls			
	Monsoon season (winter 2007)	Cristobalite, 0.02 (0.01) Quartz, 0.01 (0.01)	[18] [18]	
	Dry season (summer 2006)	Cristobalite, 0.03 (0.03) Quartz, 0.06 (0.12)	[27] [27]	
Yingratanasuk et al. (2002)		Arithmetic mean	148 (total number of samples)	Cross-sectional study design; full-shift (8-hour) personal dust samples; respirable dust analysed gravimetrically; silica analysis by infrared spectrophotometry
Stone carvers, Thailand, 1999–2000	Carvers (Site 1) Pestle makers (Site 1) Mortar makers (Site 2) Mortar makers (Site 3)	0.22 0.05 0.05 0.88		

Silica dust, crystalline (quartz or cristobalite)

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m ³)	Number of samples	Comments
Rando et al. (2001) Industrial sand industry, North America, 1974–98	Sand-processing plants	<u>Geometric mean</u> 0.042 (overall)	14249	Exposure estimates created for a longitudinal and case-referent analysis of a cohort of industrial sand workers; gravimetric analysis of total dust; silica analysis by X-ray diffraction spectroscopy
Yassin et al. (2005) Stonework masonry, USA, 1988–2003	All occupations	<u>Geometric mean (GSD)</u> 0.065 (0.732)	274	Analysis of personal silica measurements (<i>n</i> = 7209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
Foundries				
Andersson et al. (2009) Iron foundry, Sweden, April 2005–May 2006		<u>Geometric mean (GSD)</u>		Respirable dust, quartz, cristobalite, trydimite samples collected on 2 consecutive workdays for shift and daytime workers; gravimetric analysis conducted using modified NIOSH method; respirable quartz and cristobalite analysed using modified NIOSH method 7500
	Caster	0.020 (1.8)	22	
	Core Maker	0.016 (2.3)	55	
	Fettler	0.041 (2.9)	115	
	Furnace and ladle repair	0.052 (3.7)	33	
	Maintenance	0.021 (2.6)	26	
	Melter	0.022 (2.0)	49	
	Moulder	0.029 (2.6)	64	
	Sand mixer	0.020 (2.3)	14	
	Shake out	0.060 (1.7)	16	
	Transportation	0.017 (2.6)	13	
	Other	0.020 (2.0)	28	
	All occupations	0.028 (2.8)	435	

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Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m ³)	Number of samples	Comments
Yassin et al. (2005) Grey-iron foundry, USA 1988–2003	Spruer Hunter operator Charger Core maker Grinder Molder Abrasive blast operator Sorter Reline cupola Furnace operator Core setter Craneman Cleaning department Inspector Ladle repair	Geometric mean (GSD) 0.154 (0.100) 0.093 (1.144) 0.091 (0.999) 0.078 (1.033) 0.075 (0.821) 0.073 (0.910) 0.070 (0.821) 0.067 (0.827) 0.067 (0.725) 0.066 (0.766) 0.066 (0.671) 0.066 (0.815) 0.060 (0.879) 0.057 (1.298) 0.055 (0.829)	22 10 8 89 371 308 56 23 29 47 23 16 36 21 30	Analysis of personal silica measurements (<i>n</i> = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
Other metallurgical operations				
Foreland et al. (2008) Silicon carbide industry, Norway, November 2002–December 2003	Cleaning operators (Plant A) Mix operators (Plants A and C), charger/mix and charger operators (Plant C) All other jobs (Plants A, B and C) Charger/mix operators (Plant C)	Geometric mean 0.020 (quartz) 0.008–0.013 (quartz) < 0.005 (quartz) 0.038 (cristobalite)	720 (total)	Exposure survey conducted in 3 silicon carbide plants; measurements collected to improve previously developed job-exposure matrix; sampling duration close to full shift (6–8 hours); 2 sampling periods of 2 work weeks; gravimetric analysis of respirable dust; silica analysis using modified NIOSH method 7500
Construction				
Tijoe-Nij et al. (2003) Construction, the Netherlands	Concrete drillers and grinders Tuck pointers Demolition workers	Geometric mean (GSD) 0.42 (5.0) 0.35 (2.8) 0.14 (2.7)	14 10 21	Cross-sectional study design; repeated dust measurements (<i>n</i> = 67) on 34 construction workers; full-shift (6–8 hours) personal respirable dust sampling; gravimetric analysis of respirable dust; silica analysis by infrared spectroscopy (NIOSH method 7602); 8-h TWA concentrations calculated

Silica dust, crystalline (quartz or cristobalite)

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m ³)	Number of samples	Comments
Akbar-Khanzadeh & Brillhart (2002) Construction, USA	Concrete-finishing (grinding)	Arithmetic mean (SD) 1.16 (1.36)	49	Task-specific silica exposure assessment conducted as part of an OSHA Consultation Service in Ohio; gravimetric analysis of respirable samples using NIOSH method 0600; silica analysis using in-house method based on NIOSH method 7500 and OSHA ID 142
	Labourers Operating engineers Carpenters, iron workers, masons, painters, terrazzo workers	Range (min-max) 0.10-0.15 0.04-0.06 below detectable limits	20 3 17	Task-based exposure assessment conducted as part of an epidemiological study of Ontario construction workers; personal dust sampling and direct-reading particulate monitoring; gravimetric analysis of respirable dust using modified NIOSH method 0600; respirable silica analysis using modified NIOSH method 7500
Woskie et al. (2002) Heavy and highway construction, USA	Labourers	Geometric mean (GSD) 0.026 (5.9)	146	Personal samples collected using the Construction Occupational Health Program sampling strategy; particulate samples analysed gravimetrically; quartz analysed by Fourier transform infrared spectrophotometry; duration of sampling—6 hours of an 8-hour working day
	Miscellaneous trade Operating engineers	0.013 (2.8) 0.007 (2.8)	26 88	
Flanagan et al. (2003) Construction, USA, August 2000–January 2001	Clean-up, demolition with hand-held tools, concrete cutting, concrete mixing, tuck-point grinding, surface grinding, sacking and patching concrete, and concrete-floor sanding	Geometric mean (GSD) 0.11 (5.21)	113	Respirable samples analysed gravimetrically using NIOSH method 0600; silica analysed by Fourier transform infrared spectrophotometry using NIOSH method 7602
	Recess miller Demolition worker Inner wall constructor Overall	Geometric mean (GSD) 0.7 (3.3) 1.1 (4.0) 0.04 (2.6) 0.5 (5.6)	53 82 36 171	Personal air samples collected during field study at 30 construction sites; duration of sampling 3 to 4 hours; gravimetric analysis of respirable dust samples; silica analysis using NIOSH method 7500
Lumens & Spee (2001) Construction, the Netherlands				

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Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m ³)	Number of samples	Comments
Flanagan et al. (2006) Construction, USA, 1992–2002	Abrasive blasters, surface and tuck point grinders, jackhammers, rock drills	<u>Geometric mean (GSD)</u> 0.13 (5.9)	1374	Personal silica measurements collected as part of a silica-monitoring compilation project; data provided by 3 federal or state regulatory agencies (<i>n</i> = 827 samples), 6 university or research agencies (<i>n</i> = 491), and 4 private consultants or contractors (<i>n</i> = 134)
Akbar-Khanzadeh et al. (2007) Construction, USA	Uncontrolled conventional grinding Wet grinding Local exhaust ventilation grinding	<u>Arithmetic mean</u> 61.7 0.896 0.155	5 sessions 7 sessions 6 sessions	Personal samples collected during grinding operations in a controlled field laboratory to evaluate the effectiveness of wet grinding and local exhaust ventilation; samples collected and analysed using NIOSH methods 0600 and 7500
Bakke et al. (2002) Construction, Norway, 1996–99	Tunnel workers	<u>Geometric mean (GSD)</u> α -Quartz, 0.035 (5.0)	299	Personal samples collected as part of exposure survey; sampling duration: 5 to 8 h; respirable dust analysed gravimetrically; silica analysed by NIOSH method 7500
Linch (2002) Construction, USA, 1992–98	Abrasive blasting of concrete structures Drilling concrete highway pavement Concrete-wall grinding Concrete sawing Milling of asphalt	<u>TWA (8-hour)</u> 2.8 3.3 0.26 10.0 0.36		Personal samples collected as part of NIOSH effort to characterize respirable silica exposure in construction industry; respirable dust collected and analysed according to NIOSH method 0600; silica analysed by NIOSH method 7500
Meijer et al. (2001) Construction, USA, 1992–93	Concrete workers	<u>Arithmetic mean</u> 0.06	96	Personal samples of respirable dust and silica; gravimetric analysis of respirable dust; silica analysed by infrared spectrophotometry
Miscellaneous operations Hicks & Yager (2006) Coal-fired power plants, USA	Normal production activities	<u>Arithmetic mean</u> 0.048	108	Personal breathing zone samples collected during normal full shifts and analysed by NIOSH method 7500

Silica dust, crystalline (quartz or cristobalite)

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m ³)	Number of samples	Comments
Shih et al. (2008) Furnace relining, Taiwan, China	Sandblasting	<u>Arithmetic mean</u> 0.578	7	Exposures measured in a municipal waste incinerator during annual furnace relining; respirable dust collected and analysed by NIOSH method 0600; silica analysed by NIOSH method 7500
	Bottom-ash cleaning	0.386	8	
	Wall demolishing	0.116	8	
	Relining	0.041	10	
	Grid repairing	0.042	14	
	Scaffold establishing	0.040	8	
	Others	0.082	8	
		<u>Arithmetic mean</u>		
Zhuang et al. (2001) Pottery factories and metal mines, China, 1988–89	Pottery factories	0.116	54	Special exposure survey conducted to compare results obtained from traditional Chinese samplers with nylon cyclones; gravimetric analysis of cyclone samples; silica analysis using X-ray diffraction
	Iron/copper mines	0.017	23	
	Tin mines	0.097	10	
	Tungsten mines	0.101	56	
		<u>Arithmetic mean</u>		
Yassin et al. (2005) Several industries, USA, 1988–2003		<u>Geometric mean (GSD)</u>		Analysis of personal silica measurements (<i>n</i> = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
	Soap and other detergents	0.102 (0.757)	6	
	Testing laboratories services	0.099 (0.896)	53	
	Cut stone and stone products	0.091 (0.956)	405	
	General contractors	0.091 (0.900)	28	
	Coating engraving	0.075 (0.839)	75	
	Grey-iron foundries	0.073 (0.877)	1 760	
	Concrete work	0.073 (0.705)	94	
	Manufacturing explosives	0.070 (0.841)	9	
	Bridge-tunnel construction	0.070 (0.827)	91	
	Stonework masonry	0.065 (0.732)	274	
	Overall	0.073 (0.919)	7209	
		<u>Geometric mean (GSD)</u>		

GM, geometric mean; GSD, geometric standard deviation; IMIS, Integrated Management Information System; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; OSHA; SD, standard deviation

and 40 area samples were collected and analysed by X-ray diffraction. Personal samples were collected after the installation of local exhaust ventilation, and area samples were collected inside the industrial units before ($n = 20$) and after ($n = 20$) the installation of local exhaust ventilation. Personal samples were collected from process workers ($n = 12$), hopper workers ($n = 8$), drivers ($n = 11$), and office employees ($n = 9$). Personal concentrations of respirable dust were as follows: process workers, 0.21 mg/m^3 ; hopper workers, 0.45 mg/m^3 ; and, drivers, 0.20 mg/m^3 . Personal concentrations of respirable quartz were as follows: process workers, 0.19 mg/m^3 ; hopper workers, 0.40 mg/m^3 ; and, drivers, 0.17 mg/m^3 . Based on the area samples, the average levels of total dust and respirable dust were 9.46 mg/m^3 and 1.24 mg/m^3 , respectively. The amount of free silica in the stone was 85–97%.

[Golbabaie et al. \(2004\)](#) measured TWA concentrations of total dust, respirable dust, and crystalline silica (α -quartz) in a marble stone quarry located in the north-eastern region of the Islamic Republic of Iran. Full-shift (2×4 -hour samples) personal breathing zone samples were collected and analysed using gravimetric and X-ray diffraction methods. The highest levels of total and respirable dust exposure were observed for workers in the hammer drill process area (107.9 mg/m^3 and 11.2 mg/m^3 , respectively), and the cutting machine workers had the lowest levels of exposure (9.3 mg/m^3 and 1.8 mg/m^3 , respectively). The highest concentrations of α -quartz in total and respirable dust were measured in hammer drill process workers (0.670 mg/m^3 and 0.057 mg/m^3 , respectively).

In a NIOSH-conducted cohort mortality study of workers from 18 silica sand plants, [Sanderson et al. \(2000\)](#) estimated historical quartz exposures using personal respirable quartz measurements (collected during 1974–96) and impinger dust samples (collected in 1946). During 1974–96, a total of 4269 respirable dust samples were collected from workers performing

143 jobs at these 18 plants. Respirable quartz concentrations ranged from less than 1 to $11700 \text{ } \mu\text{g/m}^3$, with a geometric mean concentration of $25.9 \text{ } \mu\text{g/m}^3$. Over one-third of the samples exceeded the Mine Safety and Health Administration permissible exposure limit value for quartz (PEL, $10 \text{ mg/m}^3/(\% \text{ quartz} + 2)$), and half of the samples exceeded the NIOSH recommended exposure limit [at the time] (REL, 0.050 mg/m^3). Quartz concentrations varied significantly by plant, job, and year and decreased over time, with concentrations measured in the 1970s being significantly greater than those measured later.

(d) Foundries

[Lee \(2009\)](#) reported on exposures to benzene and crystalline silica during the inspection of a foundry processing grey and ductile iron. The facility consisted of two buildings: the main foundry where moulding, core-making, metal pouring, and shakeout took place; and, the finishing part of the site where grinding and painting was done. Personal sampling for crystalline silica was conducted in the grinding area, in casting shakeout, and in both the mould- and core-making operations. Eight-hour TWA concentrations of crystalline silica were in the range of 2.11 – 4.38 mg/m^3 in the grinding area ($n = 4$), 1.18 – 2.14 mg/m^3 in the shakeout area ($n = 2$), and 1.15 – 1.63 mg/m^3 in the core-maker area ($n = 2$). The 8-hour TWA concentration in the mould area was 0.988 mg/m^3 .

(e) Construction

In a study of cement masons at six commercial building sites in Seattle, WA, USA, [Croteau et al. \(2004\)](#) measured personal exposures to respirable dust and crystalline silica during concrete-grinding activities to assess the effectiveness of a commercially available local exhaust ventilation (LEV) system. Levels were measured with and without LEV, one sample directly after the other. A total of 28 paired

Silica dust, crystalline (quartz or cristobalite)

samples were collected. The results showed that the application of LEV resulted in a mean exposure reduction of 92%, with the overall geometric mean respirable dust exposure declining from 4.5 to 0.14 mg/m³. However, approximately one quarter of the samples collected while LEV was being used were greater than the OSHA 8-hour TWA PEL (22% of samples), and the American Conference of Governmental Industrial Hygiene (ACGIH) threshold limit value (26%) for respirable crystalline silica.

[Rappaport et al. \(2003\)](#) investigated exposures to respirable dust and crystalline silica among 80 workers in four trades (bricklayers, painters (when abrasive blasting), operating engineers, and labourers) at 36 construction sites in the Eastern and Midwestern USA. A total of 151 personal respirable air samples were collected and analysed using gravimetric and X-ray diffraction methods. Painters had the highest median exposures for respirable dust and silica (13.5 and 1.28 mg/m³, respectively), followed by labourers (2.46 and 0.350 mg/m³), bricklayers (2.13 and 3.20 mg/m³), and operating engineers (0.720 and 0.075 mg/m³). The following engineering controls and workplace characteristics were found to significantly affect silica exposures: wet dust suppression reduced labourers' exposures by approximately 3-fold; the use of ventilated cabs reduced operating engineers' exposures by approximately 6-fold; and, working indoors resulted in a 4-fold increase in labourers' exposures.

(f) Agriculture

[Archer et al. \(2002\)](#) assessed the exposure to respirable silica of 27 farm workers at seven farms in eastern North Carolina, USA. Four-hour personal breathing zone samples ($n = 37$) were collected during various agricultural activities and analysed for respirable dust, respirable silica, and percentage silica using gravimetric and X-ray diffraction methods. The overall mean respirable dust, respirable silica,

and percentage silica values were 1.31 mg/m³ ($n = 37$), 0.66 mg/m³ ($n = 34$), and 34.4% ($n = 34$), respectively. The highest respirable dust and respirable silica concentrations were measured during sweet potato transplanting (mean, 7.6 and 3.9 mg/m³, respectively; $n = 5$), and during riding on or driving an uncabbed tractor (mean, 3.1 and 1.6 mg/m³, respectively; $n = 13$).

[Nieuwenhuijsen et al. \(1999\)](#) measured personal exposure to dust, endotoxin, and crystalline silica during various agricultural operations at ten farms in California, USA, between April 1995 and June 1996. A total of 142 personal inhalable samples and 144 personal respirable samples were collected. The highest levels of inhalable dust exposure were measured during machine-harvesting of tree crops and vegetables (GM, 45.1 mg/m³ and 7.9 mg/m³, respectively), and during the cleaning of poultry houses (GM, 6.7 mg/m³). Respirable dust levels were generally low, except for machine-harvesting of tree crops and vegetables (GM, 2.8 mg/m³ and 0.9 mg/m³, respectively). The percentage of crystalline silica was higher in the respirable dust samples (overall, 18.6%; range, 4.8–23.0%) than in the inhalable dust samples (overall, 7.4%; range, not detectable to 13.0%).

(g) Miscellaneous operations

[Harrison et al. \(2005\)](#) analysed respirable silica dust samples ($n = 47$) from several Chinese workplaces (three tungsten mines, three tin mines, and nine pottery mines) to determine the effect of surface occlusion by alumino-silicate on silica particles in respirable dust. The average sample percentages of respirable-sized silica particles indicating alumino-silicate occlusion of their surface were: 45% for potteries, 18% for tin mines, and 13% for tungsten mines.

To provide a more precise estimate of the quantitative relationship between crystalline silica and lung cancer, [t Mannetje et al. \(2002\)](#) conducted a pooled analysis of existing quantitative exposure data for ten cohorts exposed to silica

(US diatomaceous earth workers; Finnish and US granite workers; US industrial sand workers; Chinese pottery workers, and tin and tungsten miners; and South African, Australian, and US gold miners). Occupation- and time-specific exposure estimates were either adopted/adapted or developed for each cohort, and converted to milligrams per cubic metre (mg/m^3) respirable crystalline silica. The median of the average cumulative exposure to respirable crystalline silica ranged from $0.04 \text{ mg}/\text{m}^3$ for US industrial sand workers to $0.59 \text{ mg}/\text{m}^3$ for Finnish granite workers. The cohort-specific median of cumulative exposure ranged from $0.13 \text{ mg}/\text{m}^3$ -years for US industrial sand workers to $11.37 \text{ mg}/\text{m}^3$ -years for Australian gold miners.

In a cross-sectional survey, [Hai et al. \(2001\)](#) determined the levels of respirable nuisance and silica dusts to which refractory brickworkers were exposed at a company in Ha Noi, Viet Nam. Respirable dust levels were in the range of 2.2 – $14.4 \text{ mg}/\text{m}^3$ at nine sample sites. The estimated free silica content of dust was 3.5% for unfired materials at the powder collectors ($n = 8$ samples), and 11.4% in the brick-cleaning area following firing ($n = 1$ sample).

[Burgess \(1998\)](#) investigated processes associated with occupational exposure to respirable crystalline silica in the British pottery industry during 1930–1995, and developed a quantitative job–exposure matrix. Exposure estimates were derived from 1390 air samples, the published literature, and unpublished reports of dust control innovations and process changes. In the matrix, daily 8-hour TWA airborne concentrations of respirable crystalline silica ranged from $0.002 \text{ mg}/\text{m}^3$ for pottery-support activities performed in the 1990s to $0.8 \text{ mg}/\text{m}^3$ for firing activities in the 1930s. Although exposure estimates within decades varied, median concentrations for all process categories displayed an overall trend towards progressive reduction in exposure during the 65 year span.

2. Cancer in Humans

2.1 Cancer of the lung

In the previous *IARC Monograph* ([IARC, 1997](#)) not all studies reviewed demonstrated an excess of cancer of the lung and, given the wide range of populations and exposure circumstances studied, some non-uniformity of results had been expected. However, overall, the epidemiological findings at the time supported an association between cancer of the lung and inhaled crystalline silica (α -quartz and cristobalite) resulting from occupational exposure.

The current evaluation has a primary focus on studies that employed quantitative data on occupational exposures to crystalline silica dust (α -quartz and cristobalite). The establishment of exposure–response relationships not only provides critical evidence of causation, but the availability of quantitative exposures on crystalline silica and other exposures of relevance facilitates the accurate assessment of exposure–response relationships in the presence of potential confounders. In addition to the focus on quantitative exposure–response relationships, a summary of findings from eight published meta-analyses of lung cancer was also elaborated. Of these, the seven meta-analyses involving absolute risk summarize the information from the many studies that did not consider quantitative exposure–response relationships, while the eighth is a meta-analysis of exposure–response.

Findings from cohort studies are given in Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.1.pdf>, and those for the case–control studies are provided in Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.2.pdf>. Given that there was concern by the previous IARC Working Group that different exposure settings (including the nature of the industry and the crystalline silica polymorph) may give rise to different (or

Silica dust, crystalline (quartz or cristobalite)

no) cancer risks, this evaluation is divided into sections based on the industrial setting where exposure to silica occurs. As with other evaluations, data from community-based studies are not included, although studies of persons with silicosis are.

2.1.1 Diatomaceous earth

Work in the diatomaceous earth industry is associated mainly with exposure to cristobalite rather than quartz, and, in the USA, is generally free of other potential confounding exposures apart from exposure to asbestos in a minority of locations. The first study of US diatomaceous earth workers revealed significant positive trends in lung cancer risk with both cumulative exposure to crystalline silica (semiquantitative) and duration of employment ([Checkoway et al., 1993](#)). Owing to concerns with confounding from asbestos, estimates of asbestos exposure were developed ([Checkoway et al., 1996](#)). Those with uncertain asbestos exposures were omitted from the analysis leading to the loss of seven lung cancer deaths. Among those with no asbestos exposure, the lung cancer standardized mortality ratios (SMR) for the two higher crystalline silica exposure groups were twice the magnitude of those for the two lowest exposure groups, although they were not significantly elevated. Rate ratios, with and without adjustment for asbestos exposure were very similar (within 2%), indicating that confounding due to asbestos was not an issue. [Checkoway et al. \(1997\)](#) provided findings from one of the two plants previously investigated but including 7 more years of follow-up as well as newly developed quantitative respirable crystalline silica exposures (Table 2.1 online). The lung cancer relative risks (RR) for the highest unlagged or 15-year exposure category were both significantly elevated. Trends for both unlagged and lagged exposure-response were of borderline significance. [Rice et al. \(2001\)](#) used the same cohort to examine risk, assessing

the relationship between lung cancer mortality and respirable crystalline silica exposure using a variety of models. All except one model demonstrated statistical significance, and the trends of the predicted rate ratios with cumulative crystalline silica exposure were generally similar across models.

A small cohort study among Icelandic diatomaceous earth workers ([Rafnsson & Gunnarsdóttir, 1997](#)) provided findings that supported an effect of crystalline silica on lung cancer risk (SIR, 2.34; 95%CI: 0.48–6.85 for those who had worked 5 or more years). Smoking habits among the workers were reported to be similar to the general population.

2.1.2 Ore mining

[Steenland & Brown \(1995\)](#) updated a cohort of US gold miners previously studied ([McDonald et al., 1978](#); Table 2.1 online). Using quantitative estimates of cumulative exposure based on particle counts, no obvious evidence of exposure-response with lung cancer mortality was observed, nor were any of the exposure category SMRs elevated. In contrast, tuberculosis and silicosis mortality was elevated and exhibited an exposure-response relationship with crystalline silica exposure.

Gold miners were investigated in a South African cohort study ([Hnizdo & Sluis-Cremer, 1991](#)) and in case-control studies nested within that cohort study and within another South African gold miner cohort ([Reid & Sluis-Cremer, 1996](#); Tables 2.1 and 2.2 online). In the [Hnizdo & Sluis-Cremer, \(1991\)](#) cohort study, lung cancer mortality was related to cumulative dust exposure when modelled as a continuous variable (respirable-surface-area-years) adjusting for smoking, as well demonstrating a monotonic increase with categories of cumulative exposures. There was also some indication of exposure-response in both case-control studies: RR, 1.12; 95%CI: 0.97–1.3 for [Reid & Sluis-Cremer \(1996\)](#),

and lung cancer mortality was elevated in the highest exposure group adjusting for smoking in the [Hnizdo et al. \(1997\)](#) study. [In this study, exposure to uranium did not confound the results.] [The Working Group noted the potential for confounding from radon, and also noted that the South African cohorts might overlap.]

[McLaughlin et al. \(1992\)](#) undertook a nested case-control study of lung cancer among the members of a prior cohort study by [Chen et al. \(1992\)](#) (Table 2.2 online). The study included workers from iron, copper, tungsten, and tin mines, and used quantitative estimates of crystalline silica dust and certain confounder exposures. Only tin miners showed a clear and substantial exposure-response relationship with the quantitative measures of crystalline silica cumulative exposure. The tin miners underwent further follow-up in a cohort study ([Chen et al., 2006](#)) and a nested case-control study ([Chen & Chen, 2002](#)). Although the cohort study findings provided some overall indication of elevated lung cancer exposure-response mortality with cumulative dust exposure (Table 2.1 online), the findings were much less clear when presented by mine and silicosis status. In the nested case-control study (Table 2.2 online), there was evidence of exposure-response with cumulative total dust exposures. There was also evidence of a relationship between lung cancer mortality and cumulative arsenic exposure, but the high correlation between arsenic and crystalline silica levels prevented mutual adjustment, and left the etiological factor unclear. The same conclusions, more generally expressed, were reported in a simple ever/never exposed approach by [Cocco et al. \(2001\)](#), and were confirmed by [Chen et al. \(2007\)](#) adjusting for smoking and other confounding factors. Here, no relationship of lung cancer mortality with cumulative crystalline silica exposure was noted for the tungsten mines, nor was any evidence for the iron and copper mines adjusting for radon. [The Working Group noted that crystalline silica exposures

were very low in the iron and copper mines.] For the tin mines, no adjustment for arsenic could be made because of its collinearity with crystalline silica exposure, but in the overall group, adjusting for smoking, arsenic, polycyclic aromatic hydrocarbons (PAHs), and radon, no exposure-response for cumulative crystalline silica exposure emerged either by quintile or through the use of a continuous predictor. This was especially true when the iron/copper mines were removed for reason of having poorer data, when the trend tended towards lower risk with increasing crystalline silica exposure.

[Carta et al. \(2001\)](#) examined 724 compensated silicotics with radiographic indication of 1/0 or greater small opacities on the International Labor Organization scale who had worked at Sardinian lead and zinc mines, brown coal mines, and granite quarries. Using quantitative estimates of cumulative exposure to respirable crystalline silica dust and radon, the exposure-response was studied in a cohort study and a nested case-control study of 34 lung cancer cases (Tables 2.1 and 2.2 online). Little evidence of a trend with crystalline silica exposure was observed in either study component (after controlling for smoking, airflow obstruction, radon, and severity of silicosis in the case-control study). A clear relationship emerged with exposure to radon in the case-control study. [The Working Group noted that this study was small.]

2.1.3 Ceramics

A case-control study of Chinese pottery workers showed evidence of elevated risk for lung cancer with exposure to crystalline silica dust, although no obvious exposure-response was seen in the three higher exposure categories ([McLaughlin et al., 1992](#); Table 2.2 online). This study was nested within the cohort analysis by [Chen et al. \(1992\)](#). Although reported exposure to asbestos was to be minimal, the workers were exposed to PAHs, and in a separate analysis

there were non-significant elevations in lung cancer risk with increasing cumulative exposure to PAHs. This was confirmed in the follow-up analysis by [Chen et al. \(2007\)](#) that found that the pottery workers had the highest PAH levels over all industrial groups. Adjustment for PAHs in the analysis led to the crystalline silica exposure relative risk of 1.1 (95%CI: 1.02–1.12) dropping to 1.0 (95%CI: 0.96–1.09). [The Working Group noted that in the prior analysis of the Chinese ceramics data by [McLaughlin et al. \(1992\)](#), adjusting for PAHs slightly raised rather than reduced the crystalline silica exposure relative risks. The correlation between the crystalline silica and PAH exposures was reported as 0.56.]

Another case-control study of pottery workers with quantitative crystalline silica dust exposures was from the United Kingdom ([Cherry et al., 1998](#)). This analysis, which was restricted to ever smokers but adjusted for smoking amount and ex-smoking, showed a significantly elevated risk of lung cancer mortality with increasing average intensity of exposure, but not with cumulative exposure. No confounders, apart from smoking, were noted in this report.

[Ulm et al. \(1999\)](#) looked at workers in the German ceramics industry, as well as the stone and quarrying industry. The study was based solely on those without silicosis, as assessed using radiographic appearances. No relationship of lung cancer mortality risk with cumulative exposure, average intensity, nor peak exposure was seen in the ceramic worker subset nor overall. [The Working Group noted that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.]

2.1.4 Quarries

In an extension of the Vermont granite workers study by [Costello & Graham \(1988\)](#), [Attfield & Costello \(2004\)](#) both lengthened the follow-up from 1982 to 1994, and developed and analysed quantitative crystalline silica dust exposures (Table 2.1 online). The exposures were noteworthy for being developed from environmental surveys undertaken throughout the period of the study. However, information on smoking and silicosis status was lacking, although confounding from other workplace exposures was likely to have been minimal or non-existent. The results showed a clear trend of increasing risk of lung cancer mortality with increasing cumulative respirable crystalline silica exposure up until the penultimate exposure group. [The Working Group noted that the findings were heavily dependent on the final exposure group; when it was included, the models were no longer statistically significant.] [Graham et al. \(2004\)](#) undertook a parallel analysis of the same data as [Attfield & Costello \(2004\)](#), but did not use quantitative exposures, and adopted essentially the same analytical approach as in their 1998 study. They concluded that there was no evidence that crystalline silica dust exposure was a risk factor for lung cancer, their main argument being that lung cancer risks were similar by duration and tenure between workers hired pre-1940 and post-1940 – periods before and following the imposition of dust controls when the crystalline silica dust levels were very different.

As noted above, [Ulm et al. \(1999\)](#) looked at workers in the German stone and quarrying industry (includes some sand and gravel workers), as well as the ceramics industry (Table 2.2 online). The study was based solely on those without silicosis, as assessed using radiographic appearances. Neither cumulative exposure, average intensity, nor peak exposure showed a relationship with lung cancer risk in the stone and quarry worker subset, nor overall. [The Working Group noted

that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.] Another study of German stone and quarry workers found an excess of lung cancer (SMR, 2.40), but no relationship between lung cancer mortality and crystalline silica exposure. [The Working Group noted that the cohort study included only 440 individuals with 16 lung cancer cases. It was also restricted to those with silicosis, which was likely to lead to a lack of low exposures, a consequent limited exposure range, and low study power.]

Among studies that did not use quantitative estimates of crystalline silica exposure, that by [Koskela et al. \(1994\)](#) is of interest because it reported that the workers had little exposure to possible confounding exposures. The risk of lung cancer was significantly elevated among those with longer duration of exposure and longer latency ($P < 0.05$). [Guénel et al. \(1989\)](#) also found an excess of lung cancer among stone workers after adjustment for smoking, but this was not the case in a study of slate workers by [Mehnert et al. \(1990\)](#).

2.1.5 Sand and gravel

Confounding from other workplace exposures is minimal in sand and gravel operations. There are three main studies of sand and gravel workers, two in North America and one in the United Kingdom. The North American studies appear to arise from the same population of workers although there is no published information on their overlap, if any. Using the basic information from the [McDonald et al. \(2001\)](#) cohort study of nine North American sand and gravel workers, [Hughes et al. \(2001\)](#)

reported significant exposure–response of lung cancer with quantitative estimates of cumulative respirable crystalline silica exposures and other related indices. [McDonald et al. \(2005\)](#) examined a slightly smaller subset of the cohort described by [McDonald et al. \(2001\)](#) based on an extended update at eight of the nine plants, and also undertook a nested case–control study. Risk of lung cancer increased monotonically with unlagged cumulative exposure ($P = 0.011$), but 15-year lagged cumulative exposures provided a slightly better fit ($P = 0.006$) (Table 2.2 online). These findings were basically similar to those obtained by [Hughes et al. \(2001\)](#) using the larger cohort and shorter follow-up time. [McDonald et al. \(2005\)](#) reported that average exposure intensity, but not years employed, showed a relationship with lung cancer risk ($P = 0.015$).

[Steenland & Sanderson \(2001\)](#) studied workers in 18 sand and gravel companies in the same trade organization as the nine included in the [McDonald et al. \(2001\)](#) study (Table 2.1 online). They, too, employed quantitative estimates of exposure derived from company records, and found indications of a relationship with lung cancer mortality, most strongly in the subset that had worked 6 or more months in the industry ($P < 0.06$). Further analysis using a nested case–control approach found marginal evidence of exposure–response using quartiles of cumulative exposure ($P = 0.04$), but stronger evidence with average intensity ($P = 0.003$). [The Working Group noted that a sensitivity analysis of the effect of smoking in this cohort ([Steenland & Greenland, 2004](#)) led to an adjusted overall SMR estimate of 1.43 (95% Monte Carlo limits: 1.15–1.78) compared with the original SMR of 1.60 (95%CI: 1.31–1.93). The analysis did not deal with the exposure–response estimates.]

The mortality experience of crystalline silica sand workers in the United Kingdom was evaluated by [Brown & Rushton \(2005b\)](#). No overall excess of lung cancer was found (although there was a large, and highly significant, variation

in lung cancer SMRs between quarries; range: 0.27–1.61, both extremes $P < 0.01$. Relative risks rose with cumulative respirable crystalline silica dust exposure in the first two quartiles, but fell below 1.0 in the highest quartile, resulting in no trend being detected. [The Working Group noted that [Steenland \(2005\)](#) commented that the low exposures in the [Brown & Rushton \(2005b\)](#) study was likely to have impacted its power to detect a crystalline-silica effect.]

2.1.6 Other industries

Two studies having quantitative exposures to crystalline silica remain, although both industries are known to be associated with exposure to other known or suspected lung carcinogens. The first, by [Watkins et al. \(2002\)](#) was a small case-control study focused on asphalt fumes and crystalline silica exposure. Crystalline silica exposures were low compared to most other studies, and there were no significant lung cancer elevations or trends with exposure (Table 2.2 online). The second study was a nested case-control analysis of Chinese iron and steel workers ([Xu et al., 1996](#)). A significant trend with cumulative total dust exposure was reported but not for cumulative crystalline silica dust exposure, although the relative risk for the highest crystalline silica-exposed group was elevated. The findings were adjusted for smoking, but not for benzo[*a*]pyrene exposures, for which the relative risks demonstrated a clear and significant trend with cumulative exposure level.

2.1.7 Semiquantitative exposure and expert-opinion studies

The studies that follow used quantitative exposure measurements in deriving crystalline silica exposure estimates for individuals but ultimately converted them to exposure scores or categories in the epidemiological analysis. [Hessel et al. \(1986\)](#) undertook a case-control study of lung cancer and cumulative crystalline silica

exposure in South African gold miners after coding the dust measurements to four discrete levels (0, 3, 6, 12). No exposure-response was detected. Neither was any evidence of exposure-response detected in the later necropsy study of South African gold miners ([Hessel et al., 1990](#)) that used the same approach to code the exposure data. [The Working Group noted that the study methods in the case-control study may have led to overmatching for exposure in the case-control study, and that there may have been some selection bias and exposure misclassification in the second study.]

[de Klerk & Musk \(1998\)](#) undertook a nested case-control analysis of lung cancer within a cohort study of gold miners and showed exposure-response for log of cumulative exposure (exposure-score-years) but not for any other index of exposure. The analysis adjusted for smoking, bronchitis, and nickel exposures, and took account of asbestos exposure. The study by [Kauppinen et al. \(2003\)](#) on road pavers found a relative risk for lung cancer of 2.26 in the highest exposure group, but there was no evidence of a linear trend of risk with level of exposure. No adjustment was made for concomitant exposures to PAHs, diesel exhaust, and asbestos, nor smoking. [Moulin et al. \(2000\)](#) conducted a nested case-control study to examine lung cancer among workers producing stainless steel and metallic alloys. Their results on 54 cases and 162 controls, adjusted for smoking but not for other confounders, indicated a marginally significant evidence of a trend with increasing crystalline silica exposure as well as with PAH exposure.

Two population-based studies that involved substantial expert opinion in assigning dust levels in developing quantitative crystalline silica exposures [Brüske-Hohlfeld et al. \(2000\)](#) and [Pukkala et al. \(2005\)](#) showed an increasing risk of lung cancer with increasing crystalline silica exposure after adjustment for smoking, and in the latter study, also for social class and exposure to asbestos.

2.1.8 Pooled analysis, meta-analyses, and other studies

[Steenland et al. \(2001\)](#) reported on a case-control analysis nested within a pooled study of data from ten cohorts from a variety of industries and countries (Table 2.2 online). It included information on diatomaceous, granite, industrial sand, and pottery workers, and workers in tungsten, tin, and gold mines. Results from all of the studies had been previously published, although not all had originally employed quantitative estimates of crystalline silica exposure; and for half, the duration of follow-up had been extended. All indices of cumulative crystalline silica exposure (cumulative, unlagged and lagged; log cumulative, unlagged and lagged) showed highly significant trends with lung cancer risk ($P < 0.0001$), and average exposure demonstrated a less significant trend ($P < 0.05$). Of these indices, log cumulative exposure led to homogeneity in findings across the cohorts ($P = 0.08$ and 0.34 for unlagged and 15-year lag respectively). Findings were similar for the mining and non-mining subgroups. No adjustment was made for smoking and other confounders, although it was noted that smoking had previously been shown not to be a major confounder in five of the ten studies. Analyses of subsets of the data omitting cohorts with suspected other confounders (radon in South African gold mines, and arsenic or PAHs in Chinese tin miners and pottery workers) did not change the overall findings. [The Working Group noted that the robustness in the findings to exclusion of cohorts with potential confounders from other occupational exposures indicates that any confounding in the individual studies were unlikely to have had an impact on their findings related to crystalline silica.]

The presence of silicosis in an individual is a biomarker of high exposure to crystalline silica dust. Accordingly, studies of individuals with silicosis have the potential to provide useful information on the lung cancer risk associated

with exposure to crystalline silica. Three meta-analyses have focused on the risk of lung cancer among individuals with silicosis ([Smith et al., 1995](#); [Tsuda et al., 1997](#); [Lacasse et al., 2005](#)). [Erren et al. \(2009\)](#) also provide summary information in an electronic supplement to their article. Four others have looked at crystalline silica exposure (including silicosis status unknown and those without silicosis; [Steenland & Stayner, 1997](#); [Kurihara & Wada, 2004](#); [Pelucchi et al., 2006](#); [Erren et al., 2009](#)). The number of studies included ranged from 11 in a meta-analysis focused on individuals without silicosis ([Erren et al., 2009](#)) to 43 ([Pelucchi et al., 2006](#)) in a study of those with and without silicosis. Reasons for this variation included: the publication date, the time period of interest, whether the study was focused on those with or without silicosis, the originating country of the studies, and analysis-specific criteria. For example, [Steenland & Stayner \(1997\)](#) rejected studies of miners and foundry workers on the assumption that they had the greatest potential for confounding exposures, and [Smith et al. \(1995\)](#) rejected certain studies they deemed under or overestimated the risk of lung cancer. Overall, of the total of 112 publications included by one or more of the seven meta-analyses, none were common to all analyses.

The detailed results from the seven meta-analyses are shown in Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.3.pdf>. In brief, all analyses except for those devoted to categories without silicosis found an elevated lung cancer risk, whether occurring among those with silicosis or among crystalline-silica-exposed workers, or arising from cohort or case-control studies. [The Working Group noted that studies that restrict their analysis to individuals without silicosis potentially limit their range of crystalline silica exposure, because individuals with the highest exposures tend to be omitted. Limiting the range of exposure results in reduced power to detect associations.] Overall, the rate ratios were

very similar across studies (1.74–2.76 for those with silicosis, and 1.25–1.32 for workers exposed to crystalline silica). Results from case–control studies, where there is greater opportunity to control for smoking, revealed lower rate ratios than from cohort studies in two analyses, greater rate ratios in two, and about the same in the fifth (the sixth analysis did not break the results out separately by study type). Moreover, the supplementary materials of [Erren *et al.* \(2009\)](#) show equal risk for crystalline silica exposure in unadjusted and smoking-adjusted studies. The two available analyses providing results on workers exposed to crystalline silica by type of study reported larger rate ratios from the case–control studies.

A further meta-analysis examined exposure–response ([Lacasse *et al.*, 2009](#)) rather than overall risk, and for this reason its findings are reported separately. The analysis included findings from ten studies having quantitative measurements of crystalline silica exposure and adjustment for smoking. An increasing risk of lung cancer was observed with increasing cumulative exposure to crystalline silica above a threshold of 1.84 mg/m³ per year. Although the overall findings were heterogeneous, they were similar to those from a subset of seven more homogeneous studies.

Many of the meta-analyses noted that a lung cancer risk was apparent either after adjusting for smoking or among non-smokers ([Smith *et al.*, 1995](#); [Tsuda *et al.*, 1997](#); [Kurihara & Wada, 2004](#); [Lacasse *et al.*, 2005](#)). [Yu & Tse \(2007\)](#) further explored the issue of smoking on the interpretation of the published cohort and case–control studies of crystalline silica exposure and lung cancer. In this, they examined reported SMRs and standardized incidence ratios (SIR) for lung cancer reported in ten different published studies, and concluded that the risk had been systematically underreported for never smokers. After adjustment, five of the ten SMRs and SIRs showed significant lung cancer excesses among never smokers compared to two when unadjusted,

and ranged from 2.60–11.93. The SMRs and SIRs for ever smokers were reduced after adjustment for smoking, but tended to retain their statistical significance.

2.2 Other cancers

2.2.1 Cancer of the stomach

In the 40 reports with information on cancer of the stomach, 18 had relative risks > 1.0 (including three significantly elevated), and 22 with relative risks ≤ 1.0 (including two significantly reduced).

2.2.2 Digestive, gastro-intestinal, or intestinal cancers

In the 15 reports of digestive, gastro-intestinal, or intestinal cancer, seven had relative risks > 1.0 (including one significantly elevated), and eight with relative risks ≤ 1.0 (two significantly reduced).

2.2.3 Cancer of the oesophagus

In the 14 reports of oesophageal cancer, five had relative risks > 1.0 (including three significantly elevated), and nine with relative risks ≤ 1.0.

[Wernli *et al.* \(2006\)](#) reported a hazard ratio of 15.80 (95%CI: 3.5–70.6) among Chinese textile workers exposed for over 10 years to crystalline silica dust. In Chinese refractory brick workers, [Pan *et al.* \(1999\)](#) found not only a significant elevation with being ever exposed to crystalline silica dust (RR, 2.75; 95%CI: 1.44–5.25), but also a clear exposure–response relationship with years of exposure, adjusting for smoking and other personal factors. [The Working Group noted that confounding from exposure to PAHs could not be ruled out in the above two studies.]

[Yu *et al.* \(2007\)](#) reported an overall SMR for cancer of the oesophagus of 2.22 (95%CI: 1.36–3.43), and an SMR of 4.21 (95%CI: 1.81–8.30)

among caisson workers (who were noted to have had higher exposures to crystalline silica dust than non-caisson workers). The relative risk of oesophageal cancer for caisson workers with silicosis was reduced to 2.34 after adjusting for smoking and alcohol drinking. No excess risk of oesophageal cancer was observed among the non-caisson workers with silicosis after adjustment.

2.2.4 Cancer of the kidney

In the eight reports on cancer of the kidney, five had relative risks > 1.0 (including two significantly elevated), and three with relative risks ≤ 1.0. The two with significantly elevated risks provided information on exposure–response relationships with crystalline silica exposure, although neither formally evaluated this. In US sand and gravel workers ([McDonald et al., 2005](#)), a non-significant negative trend with increasing crystalline silica exposure was observed. However, in Vermont granite workers ([Attfield & Costello, 2004](#)), kidney cancer SMRs increased almost monotonically with increasing exposure (except for the last exposure group), and the SMR of 3.12 in the penultimate exposure group was significantly elevated.

2.2.5 Others

There have been isolated reports of excesses in other cancers but the evidence is, in general, too sparse for evaluation. [Elci et al. \(2002\)](#) reported an excess of cancer of the larynx in workers potentially exposed to crystalline silica dust, particularly for supraglottic cancer (OR, 1.8; 95%CI: 1.3–2.3), with a significant exposure–response relationship.

2.3 Synthesis

Findings of relevance to lung cancer and crystalline silica exposure arise from five main industrial settings: ceramics, diatomaceous

earth, ore mining, quarries, and sand and gravel. Of these, the industries with the least potential for confounding are sand and gravel operations, quarries, and diatomaceous earth facilities. Among those industry segments, most studies with quantitative exposures report associations between crystalline silica exposure and lung cancer risk. The findings are supported by studies in these industries that lack quantitative exposures. Results from the other industry segments generally added support although some studies had potential confounding from arsenic, radon, or PAHs. In one case among Chinese tin miners, the arsenic and crystalline silica exposures were virtually collinear, and no adjustment could be made for arsenic. In another (Chinese pottery workers), adjustment for PAHs removed a significant crystalline silica exposure effect, and in a third, among iron and copper miners, the crystalline silica effect disappeared after adjustment for radon. In these, the role of crystalline silica exposure must be regarded as unclear. Mixed findings were reported among gold, tungsten, and lead/zinc miners.

The strongest evidence supporting the carcinogenicity of crystalline silica in the lung comes from the pooled and meta-analyses. The pooled analysis demonstrated clear exposure–response, while all of the meta-analyses strongly confirmed an overall effect of crystalline silica dust exposure despite their reliance on different studies in coming to their conclusions.

Cancers other than that of the lung have not been as thoroughly researched. In many cases the findings were reported in passing, in analyses focused on lung cancer, and rarely have the data examined exposure–response with crystalline silica exposure or its surrogates.

3. Cancer in Experimental Animals

No additional relevant cancer bioassays have been conducted since the previous *IARC Monograph* ([IARC, 1997](#)) except for a study in hamsters by inhalation ([Muhle et al., 1998](#)), and a study in mice by intratracheal instillation ([Ishihara et al., 2002](#)). Studies from the previous evaluation considered adequate are summarized below together with the new studies published since.

3.1 Inhalation exposure

See [Table 3.1](#)

3.1.1 Mouse

Female BALB/cBYJ mice exposed to crystalline silica by inhalation ([Wilson et al., 1986](#)) did not have an increase in lung tumours compared to controls. Pulmonary adenomas were observed in both the silica-exposed (9/60) and the control animals (7/59). [The Working Group noted that the study groups were small (6–16 mice).]

3.1.2 Rat

Male and female F344 rats were exposed to 0 or 52 mg/m³ of crystalline silica (Min-U-Sil) over a 24-month period. Interim removals of ten males and ten females per group were made after 4, 8, 12, and 16 months of exposure. Half of those removed were necropsied, and half were held until the end of the 24 months. None of the controls developed a lung tumour. In the silica-exposed rats, the first pulmonary tumour appeared at 494 days, and the incidence was 10/53 in females and 1/47 in males ([Dagle et al., 1986](#)).

One group of 62 female F344 rats was exposed by nose-only inhalation to 12 mg/m³ crystalline silica (Min-U-Sil) for 83 weeks. An equal number of controls was sham-exposed to filtered air, and 15 rats were left untreated. The animals were

observed for the duration of their lifespan. There were no lung tumours in the sham-exposed group, and 1/15 unexposed rats had an adenoma of the lung. In the quartz-exposed rats, the incidence of lung tumours was 18/60 ([Holland et al., 1983, 1986](#); [Johnson et al., 1987](#)).

Groups of 50 male and 50 female viral antibody-free SPF F344 rats were exposed by inhalation to 0 or 1 mg/m³ silica (DQ12; 87% crystallinity as quartz) for 24 months. The rats were then held for another 6 weeks without exposure. The incidence of lung tumours in the silica-exposed rats was 7/50 males and 12/50 in females. Only 3/100 controls had lung tumours ([Muhle et al., 1989, 1991, 1995](#)).

Three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by nose-only inhalation to 6.1 or 30.6 mg/m³ DQ12 quartz for 29 days. Interim sacrifices were made immediately after the exposure and at 6, 12, and 24 months, with the final sacrifice at 34 months after exposure. The total animals with lung tumours was 0 (controls), 37/82 (low dose), and 43/82 (high dose). Many animals had multiple tumours ([Spiethoff et al., 1992](#)).

3.1.3 Hamster

Groups of 50 male and 50 female Syrian golden hamsters were exposed to 0 (control) or 3 mg/m³ DQ12 quartz (mass median aerodynamic diameter, 1.3 µm) for 18 months. The experiment was terminated 5 months later. In the silica-exposed group, 91% of the animals developed very slight to slight fibrosis in the lung, but no significant increase of lung tumours was observed ([Muhle et al., 1998](#)).

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Table 3.1 Studies of cancer in experimental animals exposed to crystalline silica (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size, GSD	Incidence of tumours in respiratory tract	Significance	Comments
Mouse, BALB/c BYJ (F) 150, 300 or 570 d Wilson et al. (1986)	0, 1.5, 1.8 or 2.0 mg/m ³ 8 h/d, 5 d/wk 6–16 animals Diameter < 2.1 µm	Lung (adenomas): 7/59 (control), 9/60 (all exposed)	[NS]	
Rat, F344 (M, F) 24 mo Dagle et al. (1986)	0, 52 mg/m ³ 6 h/d, 5 d/wk 72/sex MMAD, 1.7–2.5 µm; GSD, 1.9–2.1	Lung (epidermoid carcinomas): M–0/42 (control), 1/47 F–0/47 (control), 10/53	[NS] [P < 0.002]	
Rat, F344 (F) Lifespan Holland et al. (1983, 1986) ; Johnson et al. (1987)	0, 12 mg/m ³ 6 h/d, 5 d/wk for 83 wk 62 animals MMAD, 2.24 µm; GSD, 1.75	Lung (tumours): 0/54 (control), 18/60 (11 adenocarcinomas, 3 squamous cell carcinomas, 6 adenomas)	[P < 0.001]	Nose-only inhalation exposure. Age unspecified
Rat, SPF F344 (M, F) 30 mo Muhle et al. (1989, 1991, 1995)	0, 1 mg/m ³ 6 h/d, 5 d/wk for 24 mo 50/sex MMAD, 1.3 µm; GSD, 1.8	Lung (tumours): 3/100 (control M, F), 7/50 (M), 12/50 (F) M–1 adenoma, 3 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours, 1 adenosquamous carcinoma, 1 squamous cell carcinoma F–2 adenomas, 8 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours	Unspecified (M) [P < 0.05] (F)	
Rat, Wistar (F) Up to 35 mo Spiethoff et al. (1992)	0, 6.1, 30.6 mg/m ³ 6 h/d, 5 d/wk for 29 d 90 animals MMAD, 1.8 µm; GSD, 2.0	0/85 (control), 37/82 (low dose), 43/82 (high dose) Multiple tumours/rat: 21 bronchiolo-alveolar adenomas, 43 bronchiolo-alveolar carcinomas, 67 squamous cell carcinomas, 1 anaplastic carcinoma	[P < 0.0001] (both doses)	Nose-only inhalation exposure

d, day or days; F, female; GSD, geometric standard deviation; h, hour or hours; M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NS, not significant; wk, week or weeks

3.2 Intranasal administration

3.2.1 Mouse

Two groups of 40 female (C57xBALB/c) F₁ mice received a single intranasal instillation of 4 mg of synthetic *d*- or *l*-quartz. A group of 60 females received an intranasal instillation of saline. Survivors were killed at 18 months after treatment, and the incidence of lymphomas and leukaemias combined was 0/60 (controls), 2/40 (*d*-quartz), and 6/40 (*l*-quartz) ([Ebbesen, 1991](#)). [The Working Group noted that the study was not designed to detect silica-induced lung tumours, and also noted the lack of information on quartz retention.]

3.3 Intratracheal administration

See [Table 3.2](#)

3.3.1 Mouse

A group of 30 male A/J mice, 11–13 weeks old, received weekly intratracheal instillations of 2.9 mg quartz for 15 weeks. A group of 20 mice received instillations of vehicle [unspecified]. Animals were killed 20 weeks after the instillations. The incidences of lung adenomas were 9/29 in the controls, and 4/20 for the silica-instilled mice, values that were not statistically different ([McNeill et al., 1990](#)).

[Ishihara et al. \(2002\)](#) administered a single dose (2 mg in saline/mouse) of crystalline silica to a group of four C57BL/6N mice by intratracheal instillation to study subsequent genotoxic effects. A control group of four animals was instilled saline only. Silicotic lesions were observed in the lungs of the exposed mice, but no pulmonary neoplasms were observed after 15 months.

3.3.2 Rat

A group of 40 Sprague Dawley rats [sex unspecified] received weekly instillations of 7 mg quartz (Min-U-Sil) in saline for 10 weeks. Another groups of 40 rats received instillations of saline alone, and 20 rats remained untreated. Animals were observed over their lifespan. The incidence of lung tumours in quartz-treated rats was 6/36, 0/40 in the saline controls, and 0/18 in the untreated rats ([Holland et al., 1983](#)).

Groups of 85 male F344 rats received a single intratracheal instillation of 20 mg quartz in deionized water, Min-U-Sil or novaculite, into the left lung. Controls were instilled with vehicle only. Interim sacrifices of ten rats were made at 6, 12, and 18 months with a final sacrifice at 22 months. The incidence of lung tumours in the Min-U-Sil-instilled rats was 30/67, in the novaculite-treated rats 21/72, and in controls 1/75. All of the lung tumours were adenocarcinomas, except for one epidermoid carcinoma in the novaculite-treated rats ([Groth et al., 1986](#)).

Groups of male and female F344/NCr rats [initial number unspecified] received one intratracheal instillation of 12 or 20 mg quartz in saline or 20 mg of ferric oxide (non-fibrogenic dust) in saline. Interim sacrifices were made at 11 and 17 months with a final sacrifice at 26 months. There was a group of untreated controls observed at unscheduled deaths after 17 months. No lung tumours were observed in the ferric-oxide-treated rats and only one adenoma was observed in the untreated controls. The high incidences of benign and mainly malignant lung tumours observed in the quartz-treated rats is summarized in [Table 3.3](#) ([Saffiotti, 1990, 1992](#); [Saffiotti et al., 1996](#)).

Six groups of 37–50 female Wistar rats, 15 weeks old, received either a single or 15 weekly intratracheal instillation of one of three types of quartz preparations in saline (see [Table 3.4](#)). A control group received 15 weekly instillations of saline. To retard the development of silicosis,

Table 3.2 Studies of cancer in experimental animals exposed to silica (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size	Incidence of tumours	Significance
Mouse, A/J (M) 20 wk McNeill et al. (1990)	0, 2.9 mg Weekly for 15 wk 30, 20 (controls) 1–5 µm (size not further specified)	Lung (adenomas): 9/29 (control), 4/20 Tumour multiplicity: 0.31 ± 0.09 (control), 0.20 ± 0.09	[NS] [NS]
Rat, Sprague Dawley (NR) Lifespan Holland et al. (1983)	0 (saline), 7 mg Weekly for 10 wk 40 animals 1.71 ± 1.86 µm	Lung (1 adenoma, 5 carcinomas): 0/40 (control), 6/36	[P<0.05] (carcinomas)
Rat, F344 (M) 22 mo Groth et al. (1986)	0, 20 mg once only 85 animals < 5 µm	Lung (adenocarcinomas): 1/75 (control), 30/67	[P<0.001]
Rat, F344/NCr (M, F) 11, 17 or 26 mo Saffioti (1990, 1992) ; Saffioti et al. (1996)	0, 12, 20 mg quartz Once only Ferric oxide (20 mg) was negative control [Initial number of rats, NR] 0.5–2.0 µm	High incidences of benign and mainly malignant lung tumours in quartz-treated rats reported in Table 3.3 No tumours observed in ferric oxide group One adenoma in untreated controls	NR
Rat, Wistar Lifespan Pott et al. (1994)	0 (saline), one single or 15 weekly injections of one of 3 types of quartz Some rats received PVNO to protect against silicosis 37–50/group	Incidences of benign and malignant lung tumours in quartz-treated rats are shown in Table 3.4 No tumours observed in saline-treated rats	NR
Hamster Syrian Golden (NR) Lifespan Holland et al. (1983)	0 (saline), 3, 7 mg quartz (Min-U-Sil) Once a wk for 10 wk 48/group; 68 (controls) 1.71 ± 1.86 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) Lifespan Renne et al. (1985)	0 (saline), 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) weekly for 15 wk 25–27/group MMAD, 5.1 µm Geometric diameter, 1.0 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) 92 wk Niemeier et al. (1986)	0 (saline), 1.1 (Sil-Co-Sil) or 0.7 (Min- U-Sil) mg One group received 3 mg ferric oxide 50/group 5 µm (Min-U-Sil)	No tumours in saline controls or in Sil-Co-Sil groups 1 adenosquamous carcinoma of the bronchi and lung in Min-U-Sil group and 1 benign tumour of the larynx in ferric oxide group	

M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NR, not reported; NS, not significant; PVNO, polyvinylpyridine-N-oxide; wk, week or weeks

Silica dust, crystalline (quartz or cristobalite)

Table 3.3 Incidence, numbers, and histological types of lung tumours in F344/NCr rats after a single intratracheal instillation of quartz

Treatment		Observation time		Lung tumours	
Material	Dose ^a			Incidence	Types
Males					
Untreated	None	17–26 mo		0/32	
Ferric oxide	20 mg	11–26 mo		0/15	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo		3/18 (17%)	6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo		6/19 (32%)	
		17–26 mo		12/14 (86%)	
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo		2/18 (11%)	5 adenomas, 14 adenocarcinomas, 1 mixed carcinoma
		Killed at 17 mo		7/19 (37%)	
		17–26 mo		7/9 (78%)	
Females					
Untreated	None	17–26 mo		1/20 (5%)	1 adenoma
Ferric oxide	20 mg	11–26 mo		0/18	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo		8/19 (42%)	2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo		10/17 (59%)	
		17–26 mo		8/9 (89%)	
	20 mg	17–26 mo		6/8 (75%)	1 adenoma, 10 adenocarcinomas, 1 mixed carcinoma, 1 epidermoid carcinoma
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo		7/18 (39%)	1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, 5 epidermoid carcinomas
		Killed at 17 mo		13/16 (81%)	
		17–26 mo		8/8 (100%)	

^a Suspended in 0.3 or 0.5 mL saline
 HF, hydrogen fluoride; mo, month or months
 From [Saffiotti \(1990, 1992\)](#), [Saffiotti et al. \(1996\)](#)

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Table 3.4 Incidence, numbers, and histological types of lung tumours in female Wistar rats after intratracheal instillation of quartz

Material	Surface area (m ² /g)	No. of instillations (del # × mg)	No. of rats examined	No. and % of rats with primary epithelial lung tumours ^a	Squamous cell carcinoma	Benign CKSCT	Total (%)	Other tumours ^b
Quartz (DQ 12)	9.4	15 × 3	37	0	1z	11	38	1
Quartz (DQ 12) + PVNO	9.4	15 × 3	38	0	1 + 3z	8 + 1x	58	2
Quartz (DQ 12)	9.4	1 × 45	40	0	1	7	23	2
Quartz (Min-U-Sil)	–	15 × 3	39	1	4 + 4z	6	54	3
Quartz (Min-U-Sil) + PVNO	–	15 × 3	35	1	2 + 1x	8	57	3
Quartz Sykron (F 600)	3.7	15 × 3	40	0	3	5	30	1
0.9% Sodium chloride	–	15 × 0.4 mL	39	0	0	0	0	5

^a If an animal was found to bear more than one primary epithelial lung tumour type, this was indicated as follows: ^xadenoma; ^yadenocarcinoma; ^zbenign CKSCT.

^b Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites

PVNO, polynitrovinylpyridine-*N*-oxide; CKSCT, cystic keratinizing squamous cell tumour

From [Pott *et al.* \(1994\)](#)

two of the groups received injections of polyvinylpyridine-*N*-oxide. All groups of quartz-exposed rats had a significant increase in lung tumours, and the rats protected against silicosis developed more pulmonary squamous cell carcinomas than rats that were not protected ([Pott et al., 1994](#)).

3.3.3 Hamster

Two groups of 48 Syrian hamsters [sex unspecified] received intratracheal instillations of 3 or 7 mg quartz (Min-U-Sil) in saline once a week for 10 weeks. A group of 68 hamsters received saline alone, and another group of 72 hamsters were untreated. All animals were observed for their lifespan. No lung tumours were observed in any of the groups ([Holland et al., 1983](#)).

Groups of 25–27 male Syrian golden hamsters, 11-weeks old, received weekly intratracheal instillation of 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) in saline for 15 weeks. Groups of 27 saline-instilled hamsters and 25 untreated controls were used as controls. Animals were observed for their lifespan. No lung tumours were observed in any group ([Renne et al., 1985](#)).

Three groups of 50 male Syrian golden hamsters received weekly instillations of 1.1 mg of quartz as Sil-Co-Sil, or 0.7 mg of quartz as Min-U-Sil, or 3 mg of ferric oxide (non-fibrogenic particle) in saline for 15 weeks. A group of 50 saline-instilled hamsters served as controls. Survivors were killed at 92 weeks after the beginning of the instillations. No respiratory tract tumours were observed in the hamsters exposed to Sil-Co-Sil or in the saline controls. One adenocarcinoma of the bronchi and lung was observed in the Min-U-Sil group, and one benign tumour of the larynx in the ferric-oxide-exposed group ([Niemeier et al., 1986](#)).

3.4 Intrapleural and intrathoracic administration

3.4.1 Mouse

One mouse study was reported in the previous *IARC Monograph* ([IARC, 1997](#)) in which the route of exposure was via a single intrathoracic injection of tridymite. The study was only reported as an abstract, and therefore is not described here ([Bryson et al., 1974](#)).

3.4.2 Rat

Two groups of 48 male and 48 female standard Wistar rats and two groups 48 male and 48 female SPF Wistar rats were given a single intrapleural injection of 20 mg alkaline-washed quartz (size, < 5 µm) in saline, and observed for their lifespan. Control rats received injections of 0.4 mL saline alone. Malignant tumours of the reticuloendothelial system involving the thoracic region were observed in 39/95 quartz-treated SPF rats [$P < 0.001$] (23 histiocytic lymphomas, five Letterer-Siwe/Hand-Schüller-Christian disease-like tumours, one lymphocytic lymphoma, four lymphoblastic lymphosarcomas, and six spindle cell sarcomas), and in 31/94 quartz-treated standard rats [$P < 0.001$] (30 histiocytic lymphomas and one spindle-cell sarcoma). In the SPF control animals, 8/96 rats had tumours (three lymphoblastic lymphosarcomas, five reticulum cell sarcomas), 7/85 standard rat controls had tumours (one lymphoblastic lymphosarcoma, and six reticulum cell sarcomas) ([Wagner & Berry, 1969](#); [Wagner, 1970](#); [Wagner & Wagner, 1972](#)). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

In a second study, with the same dosing regimen and type of quartz, 23 rats developed malignant reticuloendothelial system tumours (21 malignant lymphomas of the histiocytic type [MLHT], two thymomas, and one lymphosarcoma/thymoma/spindle cell sarcoma) in 80 male

and 80 female SPF Wistar rats after 120 weeks. In another experiment, 16 male and 16 female SPF Wistar rats dosed similarly with Min-U-Sil quartz were observed until they were moribund. Eight of the 32 rats developed MLHT and three developed thymomas/lymphosarcomas. In a last experiment with the same experimental design, 18 of 32 SPF Wistar rats that had been injected with cristobalite developed malignant lymphomas (13 MLHT and five thymomas/lymphosarcomas). No MLHT and one thymoma/lymphosarcoma tumours were observed in 15 saline-injected control rats. ([Wagner, 1976](#)). [The Working Group noted that the distribution of tumours over sexes was unspecified, and that no statistics were provided.]

In one experiment, groups of 16 male and 16 female Wistar rats were given intrapleural injections of 20 mg of four types of quartz (Min-U-Sil, D&D, Snowit, and DQ12). The animals were observed for their lifespan. For all but the group treated with DQ12 quartz, there was a statistically significant increase in MLHT over saline controls ([Table 3.5](#)). In a second experiment with the same experimental design, two other strains of rats were injected Min-U-Sil (12 male and 12 female PVG rats and 20 male and 20 female Agus rats). A non-significant increase in MLHT was observed in both strains, and there was no MLHT in the saline controls. In a third experiment with the same experimental design, cristobalite was injected, and 4/32 treated Wistar rats developed MLHT [not significant], but none of the 32 saline controls did. In a final experiment, 16 male and 16 female Wistar rats were injected triolymite (size, < 0.5 µm; 0.35x10⁶ particle/µg), and observed for their lifespan. A total of 16/32 Wistar rats developed MLHT, whereas no such tumours were observed in the 32 saline controls ([Wagner et al., 1980](#)). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

Two groups of 36 2-month-old male Sprague-Dawley rats, received a single

intrapleural injection of 20 mg DQ12 quartz in saline or saline alone, and were observed for their lifespan. Twenty-seven male rats served as untreated controls. Six malignant histiocytic lymphomas and two malignant Schwannomas were observed in the quartz-treated group [not significant], and one chronic lymphoid leukaemia and one fibrosarcoma were observed in the saline group and untreated controls, respectively ([Jaurand et al., 1987](#)).

3.5 Intraperitoneal administration

3.5.1 Rat

Two groups of 16 male and 16 female SPF Wistar rats received a single intraperitoneal injection of 20 mg of Min-U-Sil quartz in saline, and were observed for their lifespan. There were 12 saline controls [sex unspecified]. A total of 9/64 quartz-exposed rats developed malignant lymphomas (two MLHT and seven thymoma/lymphosarcomas). None of the saline controls developed MLHT, but one thymoma/lymphosarcoma was noted ([Wagner, 1976](#)). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

3.6 Subcutaneous administration

3.6.1 Mouse

Two groups of 40 female (C57xBALB/c) F₁ mice received a single subcutaneous injection of 4 mg of *d*- or *l*-quartz. A group of 60 female mice served as saline controls. At 18 months after injection, there was an incidence of lymphomas/leukemias of 0/60, 1/40 and 12/40 ($P < 0.001$), and of liver adenomas of 0/60, 1/40 and 3/40 for the saline controls, *d*-quartz and *l*-quartz groups, respectively. No injection-site tumours were reported ([Ebbesen, 1991](#)).

Silica dust, crystalline (quartz or cristobalite)

Table 3.5 Incidences of malignant lymphoma of the histiocytic type (MLHT) in Wistar rats after an intrapleural injection of 20 mg quartz/animal

Sample	No. of particles $\times 10^6/\mu\text{g}$	Size distribution (%)			Mean survival (days)	Incidence of MLHT (%) ^a
		< 1 μm	1–2 μm	2–4.6 μm		
Min-U-Sil (a commercially prepared crystalline quartz probably 93% pure)	0.59	61.4	27.9	9.1	545	11/32 (34%) ^b
D&D (obtained from Dowson & Dobson, Johannesburg, pure crystalline quartz)	0.30	48.4	33.2	18.4	633	8/32 (25%) ^b
Snowit (commercially prepared washed crystals)	1.1	81.2	12.9	5.6	653	8/32 (25%) ^b
DQ12 (standard pure quartz)	5.0	91.4	7.8	0.8	633	5/32 (16%)
Saline controls	–	–	–	–	717	0 [0/32] (0%)

^a Sex unspecified^b [Significantly different from controls by Fisher Exact test, $P < 0.05$]From [Wagner et al. \(1980\)](#)

3.7 Intravenous administration

3.7.1 Mouse

Groups of 25 male and 25 female strain A mice were injected in the tail vein with 1 mg quartz in 0.1 mL of saline, with a control group of 75 male and female untreated animals. Animals were killed 3, 4.5 or 6 months after injection. There was no difference in the incidences and multiplicities of pulmonary adenomas between treated and untreated animals ([Shimkin & Leiter, 1940](#)).

3.8 Administration with known carcinogens

3.8.1 Inhalation

(a) Rat

Studies have been completed to determine the effect of co-exposure to silica and Thorotrast, a known carcinogen (See [Table 3.6](#)). Two sets of three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by inhalation to 0, 6, or 31 mg/m³ of DQ12 quartz (mass median diameter, 1.8 μm ; GSD, 2.0) for 6 hours/day 5 days/week for 29 days. One week after the inhalation exposure,

one group of quartz-exposed rats and one group of sham-exposed rats received an intravenous injection of Thorotrast (2960 Bq ²²⁸Th/mL, 0.6 mL). Controls were only sham-exposed. In each of the six groups, interim sacrifices of three or six animals each were made 0, 6, 12 and 24 months after the end of exposure. The experiment was terminated 34 months after the end of exposure. In rats that were exposed to silica by inhalation and then given Thorotrast, there was a small increase in lung tumours compared to the already high incidence of benign and malignant tumours induced by silica alone ([Spiethoff et al., 1992](#)).

3.8.2 Intratracheal administration

(a) Rat

Four groups of white rats (group sizes varied from 28 to 70, with approximately equal numbers of males and females) were given either no treatment or a single instillation of 5 mg benzo[a]pyrene or an instillation of 50 mg quartz (size, 82% < 2 μm) and 5 mg benzo[a]pyrene (Group A) or 50 mg quartz and a later (1 month) instillation of 5 mg benzo[a]pyrene (Group B). The rats were observed until death. There were no

Table 3.6 Incidence, numbers and histological types of lung tumours in female Wistar rats after inhalation exposure to quartz and/or Thorotrast

Treatment	Number of rats ^a	Lung tumours				
		Incidence	Total number	Histological type		
		Observed		Bronchiolo-alveolar adenoma	Bronchiolo-alveolar carcinoma	Squamous cell carcinoma
Controls	85	–	–	–	–	–
Low-dose quartz	82	37	62	8	17	37
High-dose quartz	82	43	69	13	26	30
Thorotrast (Tho)	87	3	6	–	5	1
Low-dose quartz + Tho	87	39	68	10	28	30
High-dose quartz + Tho	87	57	98	16	47	35

^a Without the animals sacrificed 0 and 6 months after the end of inhalation exposure.

From [Spiethoff et al. \(1992\)](#)

lung tumours in the untreated rats (0/45), nor in those exposed to benzo[a]pyrene alone (0/19). In the combined exposures to benzo[a]pyrene and quartz, an increased incidence in lung tumours was observed (Group A, 14/31, 11 squamous cell carcinomas and three papillomas; Group B, 4/18, two papillomas and two carcinomas) ([Pylev, 1980](#)). [The Working Group noted the absence of a group exposed to quartz alone.]

(b) Hamster

Groups of 50 male Syrian golden hamsters received weekly intratracheal instillations for 15 weeks in saline of 3 mg benzo[a]pyrene or 3 mg ferric oxide or 3 mg ferric oxide plus 3 mg benzo[a]pyrene or 1.1 mg Sil-Co-Sil or 1.1 mg Sil-Co-Sil plus 3 mg benzo[a]pyrene or 0.7 mg Min-U-Sil or 0.7 mg Min-U-Sil plus 3 mg benzo[a]pyrene or 7 mg Min-U-Sil or 7 mg Min-U-Sil plus 3 mg benzo[a]pyrene. Fifty male controls received saline alone. Survivors were killed at 92 weeks after exposure. Co-exposures with silica caused an enhancement of the number of respiratory tract tumours induced by benzo[a]pyrene

(mainly in the bronchus and lung) ([Niemeier et al., 1986](#); [Table 3.7](#)).

3.9 Synthesis

Studies of the carcinogenicity of crystalline silica in experimental animal models have shown quartz dust to be a lung carcinogen in rats following inhalation and intratracheal instillation, but not in mice or hamsters. Rats are known to be more sensitive than are mice or hamsters to the induction of lung tumours due to other inhaled poorly soluble particles, such as carbon black ([Mauderly et al., 1994](#)).

Quartz-induced lymphoma incidence was also increased in several experiments in rats after intrapleural administration, and in one study in mice after subcutaneous administration. Tridymite- and cristobalite-induced lymphomas were observed in only a single experiment.

Silica dust, crystalline (quartz or cristobalite)

Table 3.7 Incidences of respiratory tract tumours in Syrian golden hamsters after intratracheal administration of quartz with or without benzo[a]pyrene

Treatment	No. of animals	No. of animals with respiratory tract tumours	No. of respiratory tract tumours ^a by site			Mean latency (wk)
			Larynx	Trachea	Bronchus and lung	
Saline control	48	0	0	0	0	–
BaP	47	22	5	3	32	72.6
Ferric oxide	50	1	1	0	0	62
Ferric oxide + BaP	48	35b,c	5	6	69	70.2
Sil-Co-Sil	50	0	0	0	0	–
Sil-Co-Sil + BaP	50	36b,c	13	13	72	66.5
Min-U-Sil	50	1	0	0	1	68
Min-U-Sil + BaP	50	44b,c	10	2	111	68.5
Min-U-Sil + ferric oxide	49	0	0	0	0	–
Min-U-Sil + ferric oxide + BaP	50	38b,c	10	4	81	66.7

^a Types of tumours: polyps, adenomas, carcinomas, squamous cell carcinomas, adenosquamous carcinomas, adenocarcinomas, sarcomas.

^b Statistically significantly higher ($P < 0.00001$; two-tailed Fisher Exact test) compared with the corresponding group not treated with BaP.

^c Statistically significantly higher ($P < 0.01$; two-tailed Fisher Exact test) compared with the BaP group.

BaP, benzo[a]pyrene

From [Niemeier et al. \(1986\)](#)

4. Other Relevant Data

4.1 Deposition and biopersistence

The inhalation of crystalline silica is associated with various lung diseases including acute silicosis or lipoproteinosis, chronic nodular silicosis, and lung cancer. Exposure to silica dust may also cause renal and autoimmune diseases ([Steenland & Goldsmith, 1995](#); [Stratta et al., 2001](#); [Cooper et al., 2002](#); [Otsuki et al., 2007](#)). In silicotic patients, alveolar macrophages collected by pulmonary lavage contain crystalline silica and at autopsy, elevated levels of quartz are found in the lungs and lymph nodes. Crystalline silica is poorly soluble and biopersistent; even after cessation of exposure, silicosis can progress and is a risk factor for the development of lung cancer ([IARC, 1997](#)).

Alveolar macrophages play a key role in silica-related toxicity, and therefore the cytotoxic potency of silica particles determine the degree of silica-related pathogenicity ([IARC,](#)

[1997](#); [Donaldson & Borm, 1998](#)). The stronger the cytotoxicity of crystalline silica to alveolar macrophages, the higher the intensity of the inflammatory reaction, and the longer the residence time of the particle in the lung ([Donaldson & Borm, 1998](#); [Fenoglio et al., 2000a](#)).

Rodent inhalation studies have investigated the relationship between intrinsic particle toxicity, persistent inflammation, altered macrophage-mediated clearance, and biopersistence in the lung ([Warheit et al., 2007](#)). Crystalline silica particles induce lung inflammation that persists even after cessation of exposure, with alveolar macrophages having reduced chemotactic responses and phagocytosis. Crystalline silica impairs macrophage-mediated clearance secondary to its cytotoxicity that allows these particles to accumulate and persist in the lungs ([IARC, 1997](#)). In humans, it is possible that co-exposure to tobacco smoke and crystalline silica may impair the clearance of these toxic particles ([IARC, 2004](#)).

4.2 Mechanisms of carcinogenicity

It is generally accepted that alveolar macrophages and neutrophils play a central role in diseases associated with exposure to crystalline silica ([Hamilton et al., 2008](#)). An inflammation-based mechanism as described in [IARC \(1997\)](#) is a likely mechanism responsible for the induction of lung cancer associated with exposure to crystalline silica, although reactive oxygen species can be directly generated by crystalline silica polymorphs themselves, and can be taken up by epithelial cells. For this reason, a direct effect on lung epithelial cells cannot be excluded ([Schins, 2002](#); [Fubini & Hubbard, 2003](#); [Knaapen et al., 2004](#)).

4.2.1 Physicochemical features of crystalline silica dusts associated with carcinogenicity

The major forms or polymorphs of crystalline silica are the natural minerals quartz, tridymite, cristobalite, coesite, stishovite, and the artificial silica-based zeolites (porosils) ([Fenoglio et al., 2000a](#)). Humans have been exposed only to quartz, tridymite, cristobalite, the other forms being very rare. Several amorphous forms of silica exist, some of which were classified in Group 3 (*not classifiable as to their carcinogenicity*) in the previous *IARC Monograph* ([IARC, 1997](#)). Also, it has been shown that this cytotoxicity is lowered with lowering hydrophilicity ([Fubini et al., 1999](#)), which depends upon the circumstances under which the surface was created. For example, silica in fly ashes or volcanic dusts is generated at high temperatures, and is mostly hydrophobic.

The classification in Group 1 (*carcinogenic to humans*) of some silica polymorphs in the previous *IARC Monograph* ([IARC, 1997](#)) was preceded by a preamble indicating that crystalline silica did not show the same carcinogenic potency in all circumstances. Physicochemical features – polymorph characteristics, associated contaminants

– may account for the differences found in humans and in experimental studies. Several studies on a large variety of silica samples, aiming to clarify the so-called “variability of quartz hazard” have indicated features and contaminants that modulate the biological responses to silica as well as several surface characteristics that contribute to the carcinogenicity of a crystalline silica particle ([Donaldson & Borm, 1998](#); [Fubini, 1998a](#); [Elias et al., 2000](#); [Donaldson et al., 2001](#)). The larger potency of freshly ground dusts (e.g. as in sandblasting) has been confirmed in several studies; [Vallyathan et al., 1995](#)), as immediately after cleavage, a large number of surface-active radicals are formed that rapidly decay ([Damm & Peukert, 2009](#)). The association with clay or other aluminium-containing compounds inhibits most adverse effects ([Duffin et al., 2001](#); [Schins et al., 2002a](#)), iron in traces may enhance the effects but an iron coverage inhibits cytotoxicity and cell transformation ([Fubini et al., 2001](#)). One study on a large variety of commercial quartz dusts has shown a spectrum of variability in oxidative stress and inflammogenicity *in vitro* and *in vivo*, which exceeds the differences previously found among different polymorphs ([Bruch et al., 2004](#); [Cakmak et al., 2004](#); [Fubini et al., 2004](#); [Seiler et al., 2004](#)). Subtle differences in the level of contaminants appear to determine such variability. New studies *in vitro* and *in vivo* on synthesized nanoparticles of quartz ([Warheit et al., 2007](#)) indicate a variability of effects also at the nanoscale. These new data clearly show that more or less pathogenic materials are comprised under the term “crystalline silica dusts.” However, most studies, so far, have failed to identify strict criteria to distinguish between potentially more or less hazardous forms of crystalline silica.

The pathogenic potential of quartz seems to be related to its surface properties, and the surface properties may vary depending on the origin of the quartz. The large variability in silica hazard even within quartz particles of the same polymorph may originate from the

Silica dust, crystalline (quartz or cristobalite)

grinding procedure, the particle shape, the thermal treatment (determines the hydrophilicity of the particle), and the metal impurities (e.g. aluminium, iron) ([Fubini et al., 2004](#)).

The toxicity of silica dust from various sources may be related either to the kind of silica polymorph or to impurities.

The correlation between artificially pure crystalline silicas (porosils) with similar physicochemical properties, but different micromorphology, size and surface area, was investigated ([Fenoglio et al., 2000a](#)). Surface area and aspect ratio (elongated crystals with a higher aspect ratio than more isometric crystals) of the particulates tested in a cellular system (mouse monocyte-macrophage tumour cell line) correlate best with inhibition of cell proliferation after 24–72 hours experimental time. From the natural crystalline silicas, only stishovite did not show a cytotoxic effect; all the other natural polymorphs were rather toxic. Stishovite is made up of smooth round particles ([Cerrato et al., 1995](#)) whereas quartz, tridymite, and cristobalite consist of particles with very sharp edges caused by grinding ([Fubini, 1998a](#); [Fubini et al., 1990, 1999](#)). Stishovite, the only polymorph with silicon in octahedral coordination, has densely packed hydroxyl-silanols on its surface that interact with hydrogen bonds with each other; for this reason, the interaction of silanols with cell membranes, which normally does occur, is dramatically reduced ([Cerrato et al., 1995](#)).

Pure silica-zeolites with different particle forms exhibit similar cytotoxicity *in vitro* if compared at equal surface area instead of equal mass. The extent of free radical generation did not show a significant correlation with cytotoxicity in this short-term in-vitro test ([Fenoglio et al., 2000a](#)). Free radicals generated by the particle may play a role in later stages of toxicity related to crystalline silica ([Ziemann et al., 2009](#)). Both silicon-based surface radicals and iron ions located at the particle surface may be active

centres for free radical release in solution ([Fubini et al., 2001](#)).

As has already been demonstrated with quartz and cristobalite ([Brown & Donaldson, 1996](#); [Bégin et al., 1987](#)), the cytotoxicity of artificially pure silica-zeolites can be decreased by aluminium ions adsorbed onto the particle surface ([Fenoglio et al., 2000a](#)). Crystalline silica may occur naturally embedded in clays or may be mixed with other materials in some commercial products. It is possible that these materials may adsorb onto the silica surface, and modify its reactivity. However, the extent of surface coverage and the potency of these modified crystalline silica particles after long-term residence in the lungs have not been systematically assessed.

A quartz sample isolated from bentonite clay obtained from a 100 to 112 million-year-old formation in Wyoming, USA, exhibits a low degree of internal crystal organization, and the surface of this quartz particles are occluded by coatings of the clay. This “quartz isolate” was compared in respect to its toxic potency after intratracheal instillation in rats with the quartz sample DQ12. The “quartz isolate” showed a much lower toxicity than DQ12 quartz, in agreement with the much lower surface reactivity of “quartz isolate” compared to the DQ12 quartz ([Creutzenberg et al., 2008](#); [Miles et al., 2008](#)).

4.2.2 Direct genotoxicity and cell transformation

Reactive oxygen species are generated not only at the particle surface of crystalline silica, but also by phagocytic and epithelial cells exposed to quartz particles ([Castranova et al., 1991](#); [Deshpande et al., 2002](#)). Oxidants generated by silica particles and by the respiratory burst of silica-activated phagocytic cells may cause cellular and lung injury, including DNA damage. Lung injury may be initiated and amplified by severe inflammation ([Donaldson et al., 2001](#); [Castranova, 2004](#); [Knaapen et al., 2004](#)). Various

products (chemotactic factors, cytokines, growth factors) released by activated (and also dying) alveolar macrophages will not only recruit more macrophages as well as polymorphonuclear leukocytes (PMNs) and lymphocytes, but may also affect and activate bronchiolar and alveolar epithelial cells.

Reactive oxygen species can directly induce DNA damage ([Knaapen et al., 2002](#); [Schins et al., 2002b](#)), and morphological transformations observed in Syrian hamster embryo (SHE) cells correlate well with the amount of hydroxyl radicals generated ([Elias et al., 2000, 2006](#); [Fubini et al., 2001](#)). Neoplastic transformation was observed in in-vitro assays in the absence of secondary inflammatory cells ([Hersterberg et al., 1986](#); [Saffiotti & Ahmed, 1995](#); [Elias et al., 2000](#)). There seems to be no correlation between the extent of cytotoxicity as assessed by colony-forming efficiency and transforming potency (SHE test) when various quartz samples were investigated ([Elias et al., 2000](#)). In contrast to transforming potency, which was clearly related to hydroxyl radical generation, cytotoxicity was not affected by antioxidants. Partial reduction of transforming potency when deferoxamine-treated quartz was used points to the role of transitional metals, e.g. iron on the particle surface in generating hydroxyl radicals ([Fubini et al., 2001](#)). The SHE test used in this study by [Fubini et al. \(2001\)](#) and by others is recommended by the Centre for the Validation of Alternative Methods (ECVAM) as an alternative method for investigating the potential carcinogenicity of particulates ([Fubini, 1998b](#)). In nude mice injected with these transformed cells, tumours could be initiated ([Saffiotti & Ahmed, 1995](#)).

Particle uptake by target cells is also relevant for direct genotoxicity ([Schins, 2002](#)). Crystalline silica particles were detected in type II lung epithelial cells (RLE-6TN) *in vitro*; these particles were located also in close proximity to the nuclei and mitochondria, but not within these organelles. An osteosarcoma cell line lacking

functional mitochondria was investigated with respect to quartz-related DNA damage with an osteosarcoma cell line with normal mitochondria. Only the cell line with functioning mitochondria showed significantly increased DNA damage after exposure to DQ12 quartz ([Li et al., 2007](#)).

The relationship between genotoxic effects (formation of DNA strand breaks) and the uptake of quartz particles was investigated *in vitro* with A549 human lung epithelial cells ([Schins et al., 2002a](#)). The percentage of A549 cells containing particles was clearly lower after exposure to quartz coated with polyvinylpyrrolidone-*N*-oxide or aluminum lactate compared to uncoated quartz (DQ12). In this experiment, DNA strand breaks measured (Comet assay) in the exposed cells correlated very well with the number of particles absorbed by the cells. It could also be demonstrated that the generation of reactive oxygen species was closely related to the formation of DNA strand breaks ([Schins, 2002](#)). However, in other in-vitro studies using different quartz species, DNA strand breaks in epithelial cells could be observed only at particle concentrations that caused cytotoxicity ([Cakmak et al., 2004](#)).

Rats were exposed to crystalline silica for 3 hours and sacrificed at different time points after exposure, and lungs were examined by electron microscopy. The lungs were fixed by vascular perfusion through the right ventricle. In these investigations, silica crystals were found within the cytoplasm of type I lung epithelial cells ([Brody et al., 1982](#)). Although type I cells are not the target cell for tumour formation, these data show that the uptake of quartz particles in epithelial lung cells *in vivo* is in principle possible. Other particles including titanium dioxide, carbon black, or metallic particles have occasionally been found in type I lung epithelial cells in rats after inhalation exposure ([Anttila, 1986](#); [Anttila et al., 1988](#); [Nolte et al., 1994](#)).

After intratracheal instillation of DQ12 quartz, DNA strand breaks could be observed in lung epithelial cells isolated from quartz-treated rats. This effect was not found when the quartz dust was treated with either polyvinylpyridine-*N*-oxide or aluminium lactate. This finding suggests an important role of the reactive surface of quartz-induced DNA damage *in vivo*. No increase in alkaline phosphatase was found in the bronchiolo-alveolar lavage fluid of quartz-treated rats, and therefore, as alkaline phosphatase is an enzyme specifically present in type II epithelial cells, it can be assumed that there was no obvious cytotoxicity in these lung cells. These data support the current view of the important role of inflammatory cells in quartz-induced genotoxic effects ([Knaapen et al., 2002](#)).

4.2.3 Depletion of antioxidant defences

Substantial amounts of ascorbic acid ([Fenoglio et al., 2000b](#)) and glutathione ([Fenoglio et al., 2003](#)) are consumed in the presence of quartz in cell-free tests via two different surface reactions. Both reactions may deplete antioxidant defences in the lung-lining fluid, thereby enhancing the extent of oxidative damage.

Incubation of murine alveolar MH-S macrophages with quartz particles (80 µg/cm²) for 24 hours inhibited glucose 6-phosphate dehydrogenase (G6PD)-1 activity by 70%, and the pentose phosphate pathway by 30%. Such effects were accompanied by a 50% decrease in intracellular glutathione. Quartz inhibits G6PD but not other oxidoreductases, and this inhibition is prevented by glutathione, suggesting that silica contributes to oxidative stress also by inhibiting the pentose phosphate pathway, which is critical for the regeneration of reduced glutathione ([Polimeni et al., 2008](#)).

4.2.4 Indirect mechanisms

After 13 weeks of inhalation exposure to 3 mg/m³ crystalline silica (mass median aerodynamic diameter, 1.3 µm) or 50 mg/m³ amorphous silica (mass median aerodynamic diameter, 0.81 µm), the percentage of PMNs in the lung of the exposed rats was similar after each exposure. However, HPRT mutation frequency of the alveolar epithelial cells was significantly increased only in rats exposed to crystalline silica. Other factors including toxic effects to epithelial cells, solubility, and biopersistence may also be important for the induction of these mutagenic effects ([Johnston et al., 2000](#)). A specific finding in rats treated intratracheally with amorphous silica (Aerosil®150, pyrogenic silica with primary particle size of 14 nm) was a severe granulomatous alveolitis which over time progressed to “scar-like” interstitial fibrotic granulomas not seen after crystalline silica exposure in rats ([Ernst et al., 2002](#)). Lung tumours were found in rats also after the repeated intratracheal instillation of the same amorphous silica ([Kolling et al., 2008](#)).

Toxic mineral dusts, especially crystalline silica, have unique, potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (silicosis) and lung cancer ([Hamilton et al., 2008](#)). Macrophages express a variety of cell-surface receptors that bind to mineral dusts leading to phagocytosis, macrophage apoptosis, or macrophage activation. The major macrophage receptor that recognizes and binds inhaled particles as well as unopsonized bacteria is MARCO ([Arredouani et al., 2004, 2005](#)). Additional members of the macrophage-scavenger receptor family responsible for binding mineral particles as well as a wide range of other ligands include SR-AI and SR-AII ([Murphy et al., 2005](#)). Although SR-AI/II and MARCO bind both toxic and non-toxic particles, only crystalline silica triggers macrophage apoptosis following

binding to these scavenger receptors ([Hamilton et al., 2008](#)). Other receptors expressed by macrophages and other target cells in the lung that bind mineral dusts include complement receptor and mannose receptors ([Gordon, 2002](#)). The pathological consequences of silica-induced injury to alveolar macrophages followed by apoptosis is impaired alveolar-macrophage-mediated clearance of crystalline silica as discussed in Section 4.1. Lysosomal membrane permeabilization following phagocytosis of crystalline silica particles has been hypothesized to enhance IL-1 β secretion ([Hornung et al., 2008](#)), and to trigger the release of cathepsin D, leading to mitochondrial damage, and the apoptosis of alveolar macrophages ([Thibodeau et al., 2004](#)). Macrophage injury and apoptosis may be responsible for the increased susceptibility of workers exposed to silica to develop autoimmune disease ([Pfau et al., 2004](#); [Brown et al., 2005](#)), and pulmonary tuberculosis ([IARC, 1997](#); [Huaux, 2007](#)).

Persistent inflammation triggered by crystalline silica (quartz) has been linked to indirect genotoxicity in lung epithelial cells in rats, see Fig. 4.1 ([IARC, 1997](#)). Rats exposed to crystalline silica develop a severe, prolonged inflammatory response characterized by elevated neutrophils, epithelial cell proliferation, and development of lung tumours ([Driscoll et al., 1997](#)). These persistent inflammatory and epithelial proliferative responses are less intense in mice and hamsters, and these species do not develop lung tumours following exposure to crystalline silica or other poorly soluble particles ([IARC, 1997](#)). There has been considerable discussion of whether the response of rats to inhaled particles is an appropriate model for the exposed response of humans ([ILSI, 2000](#)). Comparative histopathological studies of rats and humans exposed to the same particulate stimuli reveal more severe inflammation, alveolar lipoproteinosis, and alveolar epithelial hyperplasia in rats than in humans ([Green et al., 2007](#)). These studies suggest that rats are more susceptible to develop persistent

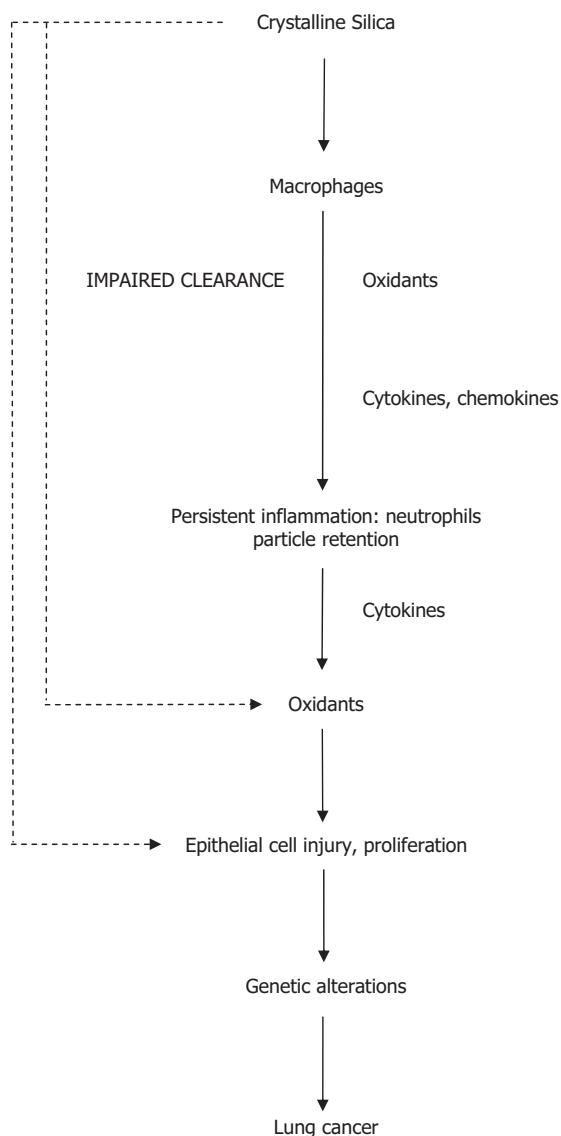
lung inflammation in response to particle inhalation than other species ([ILSI, 2000](#)).

Chronic exposure of rats to crystalline silica also leads to pulmonary fibrosis ([Oberdörster, 1996](#)), and workers with silicosis have an elevated risk of developing lung cancer ([Pelucchi et al., 2006](#)). The causal association between chronic inflammation, fibrosis, and lung cancer was reviewed by [IARC \(2002\)](#). These associations provide a biological plausible mechanism between inflammation and the development of fibrosis and/or lung cancer ([Balkwill & Mantovani, 2001](#)).

4.3 Molecular pathogenesis of cancer of the lung

Acquired molecular alterations in oncogenes and tumour-suppressor genes characterize the multistage development of lung cancer ([Sato et al., 2007](#)). Somatic alterations, such as DNA adducts, develop in the respiratory tract of smokers during the early stages of carcinogenesis ([Wiencke et al., 1999](#)). Specific point mutations in the *K-RAS* oncogene and the *p53* tumour-suppressor gene are considered as biomarkers of exposure to chemical carcinogens in tobacco smoke ([Pfeifer et al., 2002](#)). Only one study has investigated the mutational spectrum of these genes that may be used as biomarkers for exposure to crystalline silica. [Liu et al. \(2000\)](#) analysed the mutation spectra in the *K-RAS* and *p53* genes in lung cancers that developed in workers with silicosis [smoking status unknown]. In a series of 36 cases, 16 mutations in exons 5, 7 and 8 of the *p53* gene were found. In contrast to non-occupational lung cancers, seven of these mutations clustered in exon 8. Most of the *K-RAS* gene mutations in non-small cell lung carcinomas occur at codon 12. [Liu et al. \(2000\)](#) did not detect this mutation in their case series of silicotics. Six mutations were found at codon 15 in exon 1 as well as additional mutations in codons 7, 15, 20, and

Silica dust, crystalline (quartz or cristobalite)

Fig. 4.1 Proposed mechanisms for the carcinogenicity of crystalline silica in rats

21. Most of these mutations were G→C transversions in contrast to G→T transversions at codon 12, which are characteristic of non-small cell lung cancers associated with tobacco smoking. If these specific mutations are confirmed in a larger series of lung cancers in silicotics, these could provide early biomarkers for the development of lung cancer in workers exposed to crystalline silica.

In a rat model of silica-induced lung cancer, a low frequency of *p53* gene mutations and no

mutations in *K-RAS*, *N-RAS*, or *c-H-RAS* oncogenes were observed (Blanco *et al.*, 2007). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to crystalline silica.

The epigenetic silencing of the *p16^{INK4a}* (Belinsky *et al.*, 2002), *CDH13*, and *APC* genes has also been found in a rat model of lung cancer induced by intratracheal instillation of crystalline silica (Blanco *et al.*, 2007). In this rodent model, the increased expression of iNOS

(inducible nitric oxide synthase) was also found in preneoplastic lesions, which is consistent with a role for reactive nitrogen species in silicosis ([Porter et al., 2006](#)).

4.4 Species differences and susceptible populations

In rat chronic inhalation studies using crystalline silica or granular, poorly soluble particles, female rats are more susceptible than males to the induction of lung tumours. Overall, rats are susceptible to the induction of lung cancer following the exposure to crystalline silica or granular, poorly soluble particles, but hamsters and mice are more resistant. The mechanistic basis for these sex and species differences is unknown. Mice exposed to crystalline silica by intranasal instillation or subcutaneous injection, as well as rats injected intrapleurally or intraperitoneally develop lymphomas. Following inhalation exposure to crystalline silica, lymphomas have not been observed in any species (see Section 3).

In some workers exposed to crystalline silica, cytokine gene polymorphisms have been linked with silicosis ([Yucesoy et al., 2002](#)). Specific polymorphisms in genes encoding in *TNF- α* and *IL-1RA* (interleukin-1 receptor antagonist) have been associated with an increased risk for the development of silicosis ([Yucesoy & Luster, 2007](#)). Gene-linkage analyses might reveal additional markers for susceptibility to the development of silicosis and lung cancer in workers exposed to crystalline silica.

4.5 Synthesis

Three mechanisms have been proposed for the carcinogenicity of crystalline silica in rats (Fig. 4.1). First, exposure to crystalline silica impairs alveolar-macrophage-mediated particle clearance thereby increasing persistence of silica

in the lungs, which results in macrophage activation, and the sustained release of chemokines and cytokines. In rats, persistent inflammation is characterized by neutrophils that generate oxidants that induce genotoxicity, injury, and proliferation of lung epithelial cells leading to the development of lung cancer. Second, extracellular generation of free radicals by crystalline silica depletes antioxidants in the lung-lining fluid, and induces epithelial cell injury followed by epithelial cell proliferation. Third, crystalline silica particles are taken up by epithelial cells followed by intracellular generation of free radicals that directly induce genotoxicity.

The Working Group considers the first mechanism as the most prominent based on the current experimental data using inhalation or intratracheal instillation in rats, although the other mechanisms cannot be excluded. It is unknown which of these mechanisms occur in humans exposed to crystalline silica dust. The mechanism responsible for the induction of lymphomas in rats and mice following direct injections of crystalline silica dust is unknown.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of quartz dust.

There is *limited evidence* in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust.

Crystalline silica in the form of quartz or cristobalite dust is *carcinogenic to humans* (Group 1).

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References

- Akbar-Khanzadeh F & Brillhart RL (2002). Respirable crystalline silica dust exposure during concrete finishing (grinding) using hand-held grinders in the construction industry. *Ann Occup Hyg*, 46: 341–346. doi:10.1093/annhyg/mef043 PMID:12176721
- Akbar-Khanzadeh F, Milz S, Ames A *et al.* (2007). Crystalline silica dust and respirable particulate matter during indoor concrete grinding - wet grinding and ventilated grinding compared with uncontrolled conventional grinding. *J Occup Environ Hyg*, 4: 770–779. doi:10.1080/15459620701569708 PMID:17763068
- Andersson L, Bryngelsson I-L, Ohlson C-G *et al.* (2009). Quartz and dust exposure in Swedish iron foundries. *J Occup Environ Hyg*, 6: 9–18. doi:10.1080/15459620802523943 PMID:18982534
- Anttila S (1986). Dissolution of stainless steel welding fumes in the rat lung: an x ray microanalytical study. *Br J Ind Med*, 43: 592–596. PMID:3756109
- Anttila S, Grekula A, Sutinen S *et al.* (1988). Inhaled manual metal arc and shieldgas stainless and mild steel welding fumes in rat lung. *Ann Occup Hyg*, 32: 225–235.
- Archer JD, Cooper GS, Reist PC *et al.* (2002). Exposure to respirable crystalline silica in eastern North Carolina farm workers. *AIHA J (Fairfax, Va)*, 63: 750–755. doi:10.1080/15428110208984765 PMID:12570084
- Arredouani M, Yang Z, Ning Y *et al.* (2004). The scavenger receptor MARCO is required for lung defense against pneumococcal pneumonia and inhaled particles. *J Exp Med*, 200: 267–272. doi:10.1084/jem.20040731 PMID:15263032
- Arredouani MS, Palecanda A, Koziel H *et al.* (2005). MARCO is the major binding receptor for unopsonized particles and bacteria on human alveolar macrophages. *J Immunol*, 175: 6058–6064. PMID:16237101
- Attfield MD & Costello J (2004). Quantitative exposure-response for silica dust and lung cancer in Vermont granite workers. *Am J Ind Med*, 45: 129–138. doi:10.1002/ajim.10348 PMID:14748044
- Bahrami AR, Golbabai F, Mahjub H *et al.* (2008). Determination of exposure to respirable quartz in the stone crushing units at Azendarian-West of Iran. *Ind Health*, 46: 404–408. doi:10.2486/indhealth.46.404 PMID:18716390
- Bakke B, Stewart P, Eduard W (2002). Determinants of dust exposure in tunnel construction work. *Appl Occup Environ Hyg*, 17: 783–796. doi:10.1080/10473220290096032 PMID:12419106
- Balkwill F & Mantovani A (2001). Inflammation and cancer: back to Virchow? *Lancet*, 357: 539–545. doi:10.1016/S0140-6736(00)04046-0 PMID:11229684
- Bégin R, Massé S, Sébastien P *et al.* (1987). Sustained efficacy of aluminum to reduce quartz toxicity in the lung. *Exp Lung Res*, 13: 205–222. doi:10.3109/01902148709064319 PMID:2822380
- Belinsky SA, Snow SS, Nikula KJ *et al.* (2002). Aberrant CpG island methylation of the p16(INK4a) and estrogen receptor genes in rat lung tumors induced by particulate carcinogens. *Carcinogenesis*, 23: 335–339. doi:10.1093/carcin/23.2.335 PMID:11872642
- Blanco D, Vicent S, Fraga MF *et al.* (2007). Molecular analysis of a multistep lung cancer model induced by chronic inflammation reveals epigenetic regulation of p16 and activation of the DNA damage response pathway. *Neoplasia*, 9: 840–852. doi:10.1593/neo.07517 PMID:17971904
- Bråtveit M, Moen BE, Mashalla YJS, Maalim H (2003). Dust exposure during small-scale mining in Tanzania: a pilot study. *Ann Occup Hyg*, 47: 235–240. doi:10.1093/annhyg/meg027 PMID:12639837
- Brody AR, Roe MW, Evans JN, Davis GS (1982). Deposition and translocation of inhaled silica in rats. Quantification of particle distribution, macrophage participation, and function. *Lab Invest*, 47: 533–542. PMID:6292578
- Brown GM, Donaldson K (1996). *Modulation of quartz toxicity by aluminum*. In: *Silica and Silica-induced Lung Diseases*. Castranova V, Vallyathan V Wallace WE, editors. Boca Raton, FL: CRC Press, pp. 299–304.
- Brown JM, Pfau JC, Pershouse MA, Holian A (2005). Silica, apoptosis, and autoimmunity. *J Immunotoxicol*, 1: 177–187. doi:10.1080/15476910490911922 PMID:18958651
- Brown TP & Rushton L (2005a). Mortality in the UK industrial silica sand industry: 1. Assessment of exposure to respirable crystalline silica. *Occup Environ Med*, 62: 442–445. doi:10.1136/oem.2004.017715 PMID:15961619
- Brown TP & Rushton L (2005b). Mortality in the UK industrial silica sand industry: 2. A retrospective cohort study. *Occup Environ Med*, 62: 446–452. doi:10.1136/oem.2004.017731 PMID:15961620
- Bruch J, Rehn S, Rehn B *et al.* (2004). Variation of biological responses to different respirable quartz flours determined by a vector model. *Int J Hyg Environ Health*, 207: 203–216. doi:10.1078/1438-4639-00278 PMID:15330388
- Bröske-Hohlfeld I, Möhner M, Pohlabein H *et al.* (2000). Occupational lung cancer risk for men in Germany: results from a pooled case-control study. *Am J Epidemiol*, 151: 384–395. PMID:10695597
- Bryson G, Bischoff F, Stauffer RD (1974). A comparison of chrysotile and tridymite at the intrathoracic site in male Marsh mice (Abstract No. 22). *Proc Am Assoc Cancer Res*, 15: 6
- Burgess GL (1998). Development of an exposure matrix for respirable crystalline silica in the British pottery industry. *Ann Occup Hyg*, 42: 209–217. PMID:9684560

IARC MONOGRAPHS – 100C

- Cakmak GD, Schins RP, Shi T *et al.* (2004). In vitro genotoxicity assessment of commercial quartz flours in comparison to standard DQ12 quartz. *Int J Hyg Environ Health*, 207: 105–113. doi:10.1078/1438-4639-00276 PMID:15031953
- Carta P, Aru G, Manca P (2001). Mortality from lung cancer among silicotic patients in Sardinia: an update study with 10 more years of follow up. *Occup Environ Med*, 58: 786–793. doi:10.1136/oem.58.12.786 PMID:11706145
- Castranova V, Kang JH, Moore MD *et al.* (1991). Inhibition of stimulant-induced activation of phagocytic cells with tetrandrine. *J Leukoc Biol*, 50: 412–422. PMID:1655939
- Castranova V (2004). Signaling pathways controlling the production of inflammatory mediators in response to crystalline silica exposure: role of reactive oxygen/nitrogen species. *Free Radic Biol Med*, 37: 916–925. doi:10.1016/j.freeradbiomed.2004.05.032 PMID:15336307
- Cerrato G, Fubini B, Baricco M, Morterra C (1995). Spectroscopic, structural and microcalorimetric study of stishovite, a non-pathogenic polymorph of SiO₂. *J Mater Chem*, 5: 1935–1941. doi:10.1039/jm9950501935
- Checkoway H, Heyer NJ, Demers PA, Breslow NE (1993). Mortality among workers in the diatomaceous earth industry. *Br J Ind Med*, 50: 586–597. PMID:8343419
- Checkoway H, Heyer NJ, Demers PA, Gibbs GW (1996). Reanalysis of mortality from lung cancer among diatomaceous earth industry workers, with consideration of potential confounding by asbestos exposure. *Occup Environ Med*, 53: 645–647. doi:10.1136/oem.53.9.645 PMID:8882123
- Checkoway H, Heyer NJ, Seixas NS *et al.* (1997). Dose-response associations of silica with nonmalignant respiratory disease and lung cancer mortality in the diatomaceous earth industry. *Am J Epidemiol*, 145: 680–688. PMID:9125994
- Chen J, McLaughlin JK, Zhang JY *et al.* (1992). Mortality among dust-exposed Chinese mine and pottery workers. *J Occup Med*, 34: 311–316. doi:10.1097/00043764-199203000-00017 PMID:1312152
- Chen W, Bochmann F, Sun Y (2007). Effects of work related confounders on the association between silica exposure and lung cancer: a nested case-control study among Chinese miners and pottery workers. *Int Arch Occup Environ Health*, 80: 320–326. doi:10.1007/s00420-006-0137-0 PMID:16897095
- Chen W & Chen J (2002). Nested case-control study of lung cancer in four Chinese tin mines. *Occup Environ Med*, 59: 113–118. doi:10.1136/oem.59.2.113 PMID:11850554
- Chen W, Yang J, Chen J, Bruch J (2006). Exposures to silica mixed dust and cohort mortality study in tin mines: exposure-response analysis and risk assessment of lung cancer. *Am J Ind Med*, 49: 67–76. doi:10.1002/ajim.20248 PMID:16362950
- Cherry NM, Burgess GL, Turner S, McDonald JC (1998). Crystalline silica and risk of lung cancer in the potteries. *Occup Environ Med*, 55: 779–785. doi:10.1136/oem.55.11.779 PMID:9924456
- Cocco P, Rice CH, Chen JQ *et al.* (2001). Lung cancer risk, silica exposure, and silicosis in Chinese mines and pottery factories: the modifying role of other workplace lung carcinogens. *Am J Ind Med*, 40: 674–682. doi:10.1002/ajim.10022 PMID:11757044
- Cooper GS, Miller FW, Germolec DR (2002). Occupational exposures and autoimmune diseases. *Int Immunopharmacol*, 2: 303–313. doi:10.1016/S1567-5769(01)00181-3 PMID:11811933
- Costello J & Graham WG (1988). Vermont granite workers' mortality study. *Am J Ind Med*, 13: 483–497. doi:10.1002/ajim.4700130408 PMID:2834946
- Crangle RD (2009). Diatomite (advance release). In: *U.S. Geological Survey Minerals Yearbook—2008*. Reston, VA: USGS. Available at <http://minerals.usgs.gov/minerals/pubs/commodity/diatomite/myb1-2009-diato.pdf>
- Creutzenberg O, Hansen T, Ernst H *et al.* (2008). Toxicity of a quartz with occluded surfaces in a 90-day intratracheal instillation study in rats. *Inhal Toxicol*, 20: 995–1008. doi:10.1080/08958370802123903 PMID:18788017
- Croteau GA, Flanagan ME, Camp JE, Seixas NS (2004). The efficacy of local exhaust ventilation for controlling dust exposures during concrete surface grinding. *Ann Occup Hyg*, 48: 509–518. doi:10.1093/annhyg/meh050 PMID:15298850
- Dagle GE, Wehner AP, Clark ML *et al.* (1986). *Chronic inhalation exposure of rats to quartz*. In: *Silica, Silicosis and Cancer. Controversy in Occupational Medicine*. Goldsmith DR, Winn DM, Shy CM, editors. New York: Praeger, pp. 255–266. ISBN:0030041996.
- Damm C & Peukert W (2009). Kinetics of radical formation during the mechanical activation of quartz. *Langmuir*, 25: 2264–2270. doi:10.1021/la803502x PMID:19143556
- de Klerk NH & Musk AW (1998). Silica, compensated silicosis, and lung cancer in Western Australian gold-miners. *Occup Environ Med*, 55: 243–248. doi:10.1136/oem.55.4.243 PMID:9624278
- Deshpande A, Narayanan PK, Lehnert BE (2002). Silica-induced generation of extracellular factor(s) increases reactive oxygen species in human bronchial epithelial cells. *Toxicol Sci*, 67: 275–283. doi:10.1093/toxsci/67.2.275 PMID:12011487
- Dolley TP (2009). Silica (advance release). In: *U.S. Geological Survey Minerals Yearbook—2008*. Reston, VA: USGS. Available at <http://minerals.usgs.gov/minerals/pubs/commodity/silica/myb1-2008-silic.pdf>
- Donaldson K & Borm PJ (1998). The quartz hazard: a variable entity. *Ann Occup Hyg*, 42: 287–294. PMID:9729916
- Donaldson K, Stone V, Duffin R *et al.* (2001). The quartz hazard: effects of surface and matrix on inflammogenic activity. *J Environ Pathol Toxicol Oncol*, 20: Suppl 1109–118. PMID:11570668

Silica dust, crystalline (quartz or cristobalite)

- Driscoll KE, Deyo LC, Carter JM *et al.* (1997). Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells. *Carcinogenesis*, 18: 423–430. doi:10.1093/carcin/18.2.423 PMID:9054638
- Duffin R, Gilmour PS, Schins RP *et al.* (2001). Aluminium lactate treatment of DQ12 quartz inhibits its ability to cause inflammation, chemokine expression, and nuclear factor-kappaB activation. *Toxicol Appl Pharmacol*, 176: 10–17. doi:10.1006/taap.2001.9268 PMID:11578144
- Ebbesen P (1991). Chirality of quartz. Fibrosis and tumour development in dust inoculated mice. *Eur J Cancer Prev*, 1: 39–42. doi:10.1097/00008469-199110000-00008 PMID:1842682
- Elci OC, Akpınar-Elci M, Blair A, Dosemeci M (2002). Occupational dust exposure and the risk of laryngeal cancer in Turkey. *Scand J Work Environ Health*, 28: 278–284. PMID:12199430
- Elias Z, Poirot O, Danière MC *et al.* (2000). Cytotoxic and transforming effects of silica particles with different surface properties in Syrian hamster embryo (SHE) cells. *Toxicol In Vitro*, 14: 409–422. doi:10.1016/S0887-2333(00)00039-4 PMID:10963957
- Elias Z, Poirot O, Fenoglio I *et al.* (2006). Surface reactivity, cytotoxic, and morphological transforming effects of diatomaceous Earth products in Syrian hamster embryo cells. *Toxicol Sci*, 91: 510–520. doi:10.1093/toxsci/kfj177 PMID:16571621
- Ernst H, Rittinghausen S, Bartsch W *et al.* (2002). Pulmonary inflammation in rats after intratracheal instillation of quartz, amorphous SiO₂, carbon black, and coal dust and the influence of poly-2-vinylpyridine-N-oxide (PVNO). *Exp Toxicol Pathol*, 54: 109–126. doi:10.1078/0940-2993-00241 PMID:12211632
- Erren TC, Glende CB, Morfeld P, Piekarski C (2009). Is exposure to silica associated with lung cancer in the absence of silicosis? A meta-analytical approach to an important public health question. *Int Arch Occup Environ Health*, 82: 997–1004. PMID:19066933
- Fenoglio I, Croce A, Di Renzo F *et al.* (2000a). Pure-silica zeolites (Porosils) as model solids for the evaluation of the physicochemical features determining silica toxicity to macrophages. *Chem Res Toxicol*, 13: 489–500. doi:10.1021/tx990169u PMID:10858322
- Fenoglio I, Fonsato S, Fubini B (2003). Reaction of cysteine and glutathione (GSH) at the freshly fractured quartz surface: a possible role in silica-related diseases? *Free Radic Biol Med*, 35: 752–762. doi:10.1016/S0891-5849(03)00398-8 PMID:14583339
- Fenoglio I, Martra G, Coluccia S, Fubini B (2000b). Possible role of ascorbic acid in the oxidative damage induced by inhaled crystalline silica particles. *Chem Res Toxicol*, 13: 971–975. doi:10.1021/tx000125h PMID:11080045
- Flanagan ME, Seixas N, Becker P *et al.* (2006). Silica exposure on construction sites: results of an exposure monitoring data compilation project. *J Occup Environ Hyg*, 3: 144–152. doi:10.1080/15459620500526552 PMID:16464818
- Flanagan ME, Seixas N, Majar M *et al.* (2003). Silica dust exposures during selected construction activities. *AIHAJ*, 64: 319–328. PMID:12809537.
- Førelund S, Bye E, Bakke B, Eduard W (2008). Exposure to fibres, crystalline silica, silicon carbide and sulphur dioxide in the Norwegian silicon carbide industry. *Ann Occup Hyg*, 52: 317–336. doi:10.1093/annhyg/men029 PMID:18550624
- Fubini B (1998a). Surface chemistry and quartz hazard. *Ann Occup Hyg*, 42: 521–530. PMID:9838865
- Fubini B (1998b). Non-animal Tests for Evaluating the Toxicity of Solid Xenobiotics. *Atla*, 26: 579–617.
- Fubini B, Fenoglio I, Ceschino R *et al.* (2004). Relationship between the state of the surface of four commercial quartz flours and their biological activity in vitro and in vivo. *Int J Hyg Environ Health*, 207: 89–104. doi:10.1078/1438-4639-00277 PMID:15031952
- Fubini B, Fenoglio I, Elias Z, Poirot O (2001). Variability of biological responses to silicas: effect of origin, crystallinity, and state of surface on generation of reactive oxygen species and morphological transformation of mammalian cells. *J Environ Pathol Toxicol Oncol*, 20: Suppl 195–108. PMID:11570678
- Fubini B, Giamello E, Volante M *et al.* (1990). Chemical functionalities at the silica surface determining its reactivity when inhaled. Formation and reactivity of surface radicals. *Toxicol Ind Health*, 6: 571–598. PMID:1670383.
- Fubini B & Hubbard A (2003). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis. *Free Radic Biol Med*, 34: 1507–1516. doi:10.1016/S0891-5849(03)00149-7 PMID:12788471
- Fubini B, Zanetti G, Altília S *et al.* (1999). Relationship between surface properties and cellular responses to crystalline silica: studies with heat-treated cristobalite. *Chem Res Toxicol*, 12: 737–745. doi:10.1021/tx980261a PMID:10458708
- Golbabaie F, Barghi M-A, Sakhaei M (2004). Evaluation of workers' exposure to total, respirable and silica dust and the related health symptoms in Senjedak stone quarry, Iran. *Ind Health*, 42: 29–33. doi:10.2486/indhealth.42.29 PMID:14964615
- Gordon S (2002). Pattern recognition receptors: doubling up for the innate immune response. *Cell*, 111: 927–930. doi:10.1016/S0092-8674(02)01201-1 PMID:12507420
- Gottesfeld P, Nicas M, Kephart JW *et al.* (2008). Reduction of respirable silica following the introduction of water spray applications in Indian stone crusher mills. *Int J Occup Environ Health*, 14: 94–103. PMID:18507285
- Graham WG, Costello J, Vacek PM (2004). Vermont granite mortality study: an update with an emphasis on lung cancer. *J Occup Environ Med*, 46:

IARC MONOGRAPHS – 100C

- 459–466. doi:10.1097/01.jom.0000126026.22470.6d PMID:15167394
- Green FH, Vallyathan V, Hahn FF (2007). Comparative pathology of environmental lung disease: an overview. *Toxicol Pathol*, 35: 136–147. doi:10.1080/01926230601132055 PMID:17325982
- Groth DH, Stettler LE, Platek SF *et al.* (1986). Lung tumors in rats treated with quartz by instillation. In: *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Goldsmith DR, Winn DM, Shy CM, editors. New York: Praeger, pp. 243–253. ISBN:0030041996.
- Guénel P, Breum NO, Lynge E (1989). Exposure to silica dust in the Danish stone industry. *Scand J Work Environ Health*, 15: 147–153. PMID:2549615
- Hai DN, Chai SK, Chien VC *et al.* (2001). An occupational risk survey of a refractory brick company in Ha Noi, Viet Nam. *Int J Occup Environ Health*, 7: 195–200. PMID:11513069
- Hamilton RF Jr, Thakur SA, Holian A (2008). Silica binding and toxicity in alveolar macrophages. *Free Radic Biol Med*, 44: 1246–1258. doi:10.1016/j.freeradbiomed.2007.12.027 PMID:18226603
- Harrison J, Chen J-Q, Miller W *et al.* (2005). Risk of silicosis in cohorts of Chinese tin and tungsten miners and pottery workers (II): Workplace-specific silica particle surface composition. *Am J Ind Med*, 48: 10–15. doi:10.1002/ajim.20175 PMID:15940714
- Hayumbu P, Robins TG, Key-Schwartz R (2008). Cross-sectional silica exposure measurements at two Zambian copper mines of Nkana and Mufulira. *Int J Environ Res Public Health*, 5: 86–90. PMID:18678921
- Hersterberg TW, Oshimura M, Brody AR *et al.* (1986). Asbestos and silica induce morphological transformation of mammalian cells in culture: a possible mechanism. In: *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Goldsmith DR, Winn DM, Shy CM, editors. New York: Praeger, pp. 177–190.
- Hessel PA, Sluis-Cremer GK, Hnizdo E (1986). Case-control study of silicosis, silica exposure, and lung cancer in white South African gold miners. *Am J Ind Med*, 10: 57–62. doi:10.1002/ajim.4700100107 PMID:3017101
- Hessel PA, Sluis-Cremer GK, Hnizdo E (1990). Silica exposure, silicosis, and lung cancer: a necropsy study. *Br J Ind Med*, 47: 4–9. PMID:2155648
- Hicks J & Yager J (2006). Airborne crystalline silica concentrations at coal-fired power plants associated with coal fly ash. *J Occup Environ Hyg*, 3: 448–455. doi:10.1080/15459620600802747 PMID:16862716
- Hnizdo E, Murray J, Klempman S (1997). Lung cancer in relation to exposure to silica dust, silicosis and uranium production in South African gold miners. *Thorax*, 52: 271–275. doi:10.1136/thx.52.3.271 PMID:9093345
- Hnizdo E & Sluis-Cremer GK (1991). Silica exposure, silicosis, and lung cancer: a mortality study of South African gold miners. *Br J Ind Med*, 48: 53–60. PMID:1847069
- Holland L, Gonzales M, Wilson J (1983). *Pulmonary effects of shale dusts in experimental animals*. In: *Health Issues Related to Metal and Nonmetallic Mining*. Wagner W, Rom W, Merchand J, editors. Boston MA: Butterworths, pp. 485–496. ISBN:0250406101.
- Holland L, Wilson J MI, Tillery M (1986). Lung cancer in rats exposed to fibrogenic dusts. In: *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Goldsmith DR, Winn DM, Shy CM, editors. New York: Praeger, pp. 267–279. ISBN:0030041996.
- Hornung V, Bauernfeind F, Halle A *et al.* (2008). Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol*, 9: 847–856. doi:10.1038/ni.1631 PMID:18604214
- Huax F (2007). New developments in the understanding of immunology in silicosis. *Curr Opin Allergy Clin Immunol*, 7: 168–173. doi:10.1097/ACI.0b013e32802bf8a5 PMID:17351471
- Hughes JM, Weill H, Rando RJ *et al.* (2001). Cohort mortality study of North American industrial sand workers. II. Case-referent analysis of lung cancer and silicosis deaths. *Ann Occup Hyg*, 45: 201–207. PMID:11295143
- IARC (1987a). Silica and some silicates. *IARC Monogr Eval Carcinog Risk Chem Hum*, 42: 1–239. PMID:2824337
- IARC (1987b). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203
- IARC (1997). Silica, some silicates, coal dust and para-aramid fibrils. *IARC Monogr Eval Carcinog Risks Hum*, 68: 1–475. PMID:9303953
- IARC (2002). Man-made vitreous fibres. *IARC Monogr Eval Carcinog Risks Hum*, 81: 1–381. PMID:12458547
- IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, 83: 1–1438. PMID:15285078
- ILSI; Risk Science Institute Workshop Participants. (2000). The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. *Inhal Toxicol*, 12: 1–17. PMID:10715616
- Ishihara Y, Iijima H, Matsunaga K *et al.* (2002). Expression and mutation of p53 gene in the lung of mice intratracheal injected with crystalline silica. *Cancer Lett*, 177: 125–128. doi:10.1016/S0304-3835(01)00779-0 PMID:11825659
- Jaurand MC, Fleury J, Monchaux G *et al.* (1987). Pleural carcinogenic potency of mineral fibers (asbestos, attapulgite) and their cytotoxicity on cultured cells. *J Natl Cancer Inst*, 79: 797–804. PMID:2821313
- Johnson NF, Smith DM, Sebring R, Holland LM (1987). Silica-induced alveolar cell tumors in rats. *Am J*

Silica dust, crystalline (quartz or cristobalite)

- Ind Med*, 11: 93–107. doi:10.1002/ajim.4700110110 PMID:3028139
- Johnston CJ, Driscoll KE, Finkelstein JN *et al.* (2000). Pulmonary chemokine and mutagenic responses in rats after subchronic inhalation of amorphous and crystalline silica. *Toxicol Sci*, 56: 405–413. doi:10.1093/toxsci/56.2.405 PMID:10911000
- Kauppinen T, Heikkilä P, Partanen T *et al.* (2003). Mortality and cancer incidence of workers in Finnish road paving companies. *Am J Ind Med*, 43: 49–57. doi:10.1002/ajim.10161 PMID:12494421
- Kauppinen T, Toikkanen J, Pedersen D *et al.* (2000). Occupational exposure to carcinogens in the European Union. *Occup Environ Med*, 57: 10–18. doi:10.1136/oem.57.1.10 PMID:10711264
- Knaapen AM, Albrecht C, Becker A *et al.* (2002). DNA damage in lung epithelial cells isolated from rats exposed to quartz: role of surface reactivity and neutrophilic inflammation. *Carcinogenesis*, 23: 1111–1120. doi:10.1093/carcin/23.7.1111 PMID:12117767
- Knaapen AM, Borm PJ, Albrecht C, Schins RP (2004). Inhaled particles and lung cancer. Part A: Mechanisms. *Int J Cancer*, 109: 799–809. doi:10.1002/ijc.11708 PMID:15027112
- Kolling A, Ernst H, Rittinghausen S *et al.* (2008). Comparison of primary lung tumor incidences in the rat evaluated by the standard microscopy method and by multiple step sections. *Exp Toxicol Pathol*, 60: 281–288. doi:10.1016/j.etp.2008.02.003 PMID:18455915
- Koskela RS, Klockars M, Laurent H, Holopainen M (1994). Silica dust exposure and lung cancer. *Scand J Work Environ Health*, 20: 407–416. PMID:7701286
- Kurihara N & Wada O (2004). Silicosis and smoking strongly increase lung cancer risk in silica-exposed workers. *Ind Health*, 42: 303–314. doi:10.2486/indhealth.42.303 PMID:15295901
- Lacasse Y, Martin S, Gagné D, Lakhal L (2009). Dose-response meta-analysis of silica and lung cancer. *Cancer Causes Control*, 20: 925–933. doi:10.1007/s10552-009-9296-0 PMID:19184475
- Lacasse Y, Martin S, Simard S, Desmeules M (2005). Meta-analysis of silicosis and lung cancer. *Scand J Work Environ Health*, 31: 450–458. PMID:16425586
- Lee K (2009). OSHA compliance issues: benzene and crystalline silica exposures in a grey iron foundry. *J Occup Environ Hyg*, 6: D15–D17. doi:10.1080/15459620902754380 PMID:19205997
- Li H, Haberzettl P, Albrecht C *et al.* (2007). Inhibition of the mitochondrial respiratory chain function abrogates quartz induced DNA damage in lung epithelial cells. *Mutat Res*, 617: 46–57. PMID:17239409
- Linch KD (2002). Respirable concrete dust–silicosis hazard in the construction industry. *Appl Occup Environ Hyg*, 17: 209–221. doi:10.1080/104732202753438298 PMID:11871757
- Liu B, Guan R, Zhou P *et al.* (2000). A distinct mutational spectrum of p53 and K-ras genes in lung cancer of workers with silicosis. *J Environ Pathol Toxicol Oncol*, 19: 1–7. PMID:10905501
- Lumens MEGL & Spee T (2001). Determinants of exposure to respirable quartz dust in the construction industry. *Ann Occup Hyg*, 45: 585–595. PMID:11583660
- Mauderly JL, Snipes MB, Barr EB *et al.* (1994). Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats. Part I: Neoplastic and nonneoplastic lung lesions. *Res Rep Health Eff Inst*, (68, Pt 1): 1–75, discussion 77–97. PMID:7530965
- Mamuya SHD, Bråtveit M, Mwaiselage J *et al.* (2006). High exposure to respirable dust and quartz in a labour-intensive coal mine in Tanzania. *Ann Occup Hyg*, 50: 197–204. doi:10.1093/annhyg/mei052 PMID:16143714
- McDonald AD, McDonald JC, Rando RJ *et al.* (2001). Cohort mortality study of North American industrial sand workers. I. Mortality from lung cancer, silicosis and other causes. *Ann Occup Hyg*, 45: 193–199. PMID:11295142
- McDonald JC, Gibbs GW, Liddell FD, McDonald AD (1978). Mortality after long exposure to cumingtonite-grunerite. *Am Rev Respir Dis*, 118: 271–277. PMID:211890
- McDonald JC, McDonald AD, Hughes JM *et al.* (2005). Mortality from lung and kidney disease in a cohort of North American industrial sand workers: an update. *Ann Occup Hyg*, 49: 367–373. doi:10.1093/annhyg/mei001 PMID:15728107
- McLaughlin JK, Chen JQ, Dosemeci M *et al.* (1992). A nested case–control study of lung cancer among silica exposed workers in China. *Br J Ind Med*, 49: 167–171. PMID:1313281
- McNeill DA, Chrisp CE, Fisher GL (1990). Pulmonary adenomas in A/J mice treated with silica. *Drug Chem Toxicol*, 13: 87–92. doi:10.3109/01480549009011071 PMID:2165900
- Mehnert WH, Staneczek W, Möhner M *et al.* (1990). A mortality study of a cohort of slate quarry workers in the German Democratic Republic. *IARC Sci Publ*, (97): 55–64. PMID:2164503
- Meijer E, Kromhout H, Heederik D (2001). Respiratory effects of exposure to low levels of concrete dust containing crystalline silica. *Am J Ind Med*, 40: 133–140. doi:10.1002/ajim.1080 PMID:11494340
- Miles W, Moll WF, Hamilton RD, Brown RK (2008). Physicochemical and mineralogical characterization of test materials used in 28-day and 90-day intratracheal instillation toxicology studies in rats. *Inhal Toxicol*, 20: 981–993. doi:10.1080/08958370802077943 PMID:18686105
- Mirabelli D & Kauppinen T (2005). Occupational exposures to carcinogens in Italy: an update of CAREX database. *Int J Occup Environ Health*, 11: 53–63. PMID:15859192

IARC MONOGRAPHS – 100C

- Moulin JJ, Clavel T, Roy D *et al.* (2000). Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int Arch Occup Environ Health*, 73: 171–180. doi:10.1007/s004200050024 PMID:10787132
- Muhle H, Bellman B, Creutzenberg O *et al.* (1998). Pulmonary response to toner TiO₂ and crystalline silica upon chronic inhalation exposure in syrian golden hamsters. *Inhal Toxicol*, 10: 667–729.
- Muhle H, Bellmann B, Creutzenberg O *et al.* (1991). Pulmonary response to toner upon chronic inhalation exposure in rats. *Fundam Appl Toxicol*, 17: 280–299. doi:10.1016/0272-0590(91)90219-T PMID:1662648
- Muhle H, Kittel B, Ernst H *et al.* (1995). Neoplastic lung lesions in rat after chronic exposure to crystalline silica. *Scand J Work Environ Health*, 21: Suppl 227–29. PMID:8929684
- Muhle H, Takenaka S, Mohr U *et al.* (1989). Lung tumor induction upon long-term low-level inhalation of crystalline silica. *Am J Ind Med*, 15: 343–346. PMID:2539015
- Murphy JE, Tedbury PR, Homer-Vanniasinkam S *et al.* (2005). Biochemistry and cell biology of mammalian scavenger receptors. *Atherosclerosis*, 182: 1–15. doi:10.1016/j.atherosclerosis.2005.03.036 PMID:15904923
- Naidoo R, Seixas N, Robins T (2006). *Estimation of respirable dust exposure among coal miners*, in South Africa. *J Occup Environ Hyg*, 3: 293–300. doi:10.1080/15459620600668973 PMID:15859192
- Niemeier R, Mulligan LT, Rowland J (1986). *Cocarcinogenicity of foundry silica sand in hamsters*. In: *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Goldsmith DR, Winn DM, Shy CM, editors. New York: Praeger, pp. 215–227. ISBN:0030041996.
- Nieuwenhuijsen MJ, Noderer KS, Schenker MB *et al.* (1999). Personal exposure to dust, endotoxin and crystalline silica in California agriculture. *Ann Occup Hyg*, 43: 35–42. PMID:10028892
- NIOSH (2002). *NIOSH Hazard Review: Health Effects of Occupational Exposure to Respirable Crystalline Silica* (DHHS (NIOSH) Publication No. 2002–129). Cincinnati, OH, 145 pp.
- Nolte T, Thiedemann KU, Dungworth DL *et al.* (1994). Histological and Ultrastructural Alterations of the Bronchioloalveolar Region in the Rat Lung After Chronic Exposure to a Pyrolyzed Pitch Condensate or Carbon Black, Alone or in Combination. *Inhal Toxicol*, 6: 459–483. doi:10.3109/08958379409040505
- NTP (2005). *Report on Carcinogens, Eleventh Edition. Silica, Crystalline (Respirable Size*)*. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.
- Oberdörster G (1996). Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. *Inhal Toxicol*, 8: Suppl73–89. PMID:11542496
- Otsuki T, Maeda M, Murakami S *et al.* (2007). Immunological effects of silica and asbestos. *Cell Mol Immunol*, 4: 261–268. PMID:17764616
- Pan G, Takahashi K, Feng Y *et al.* (1999). Nested case-control study of esophageal cancer in relation to occupational exposure to silica and other dusts. *Am J Ind Med*, 35: 272–280. doi:10.1002/(SICI)1097-0274(199903)35:3<272::AID-AJIM7>3.0.CO;2-T PMID:9987560
- Park R, Rice F, Stayner L *et al.* (2002). Exposure to crystalline silica, silicosis, and lung disease other than cancer in diatomaceous earth industry workers: a quantitative risk assessment. *Occup Environ Med*, 59: 36–43. doi:10.1136/oem.59.1.36 PMID:11836467
- Pelucchi C, Pira E, Piolatto G *et al.* (2006). Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996–2005. *Ann Oncol*, 17: 1039–1050. doi:10.1093/annonc/mdj125 PMID:16403810
- Pfau JC, Brown JM, Holian A (2004). Silica-exposed mice generate autoantibodies to apoptotic cells. *Toxicology*, 195: 167–176. doi:10.1016/j.tox.2003.09.011 PMID:14751672
- Pfeifer GP, Denissenko MF, Olivier M *et al.* (2002). Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene*, 21: 7435–7451. doi:10.1038/sj.onc.1205803 PMID:12379884
- Polimeni M, Gazzano E, Ghiazza M *et al.* (2008). Quartz inhibits glucose 6-phosphate dehydrogenase in murine alveolar macrophages. *Chem Res Toxicol*, 21: 888–894. doi:10.1021/tx7003213 PMID:18370412
- Porter DW, Millecchia LL, Willard P *et al.* (2006). Nitric oxide and reactive oxygen species production causes progressive damage in rats after cessation of silica inhalation. *Toxicol Sci*, 90: 188–197. doi:10.1093/toxsci/kfj075 PMID:16339787
- Pott F, Dungworth DL, Einrich U *et al.* (1994). Lung tumours in rats after intratracheal instillation of dusts. *Ann Occup Hyg*, 38: Suppl. 1357–363.
- Pukkala E, Guo J, Kyyrönen P *et al.* (2005). National job-exposure matrix in analyses of census-based estimates of occupational cancer risk. *Scand J Work Environ Health*, 31: 97–107. PMID:15864903
- Pylev LN (1980). Role of silicon dioxide in the development of lung tumors induced in rats by intratracheal administration of benz(a)pyrene *Gig Tr Prof Zabol*, (4): 33–36. PMID:6250952
- Rafnsson V & Gunnarsdóttir H (1997). Lung cancer incidence among an Icelandic cohort exposed to diatomaceous earth and cristobalite. *Scand J Work Environ Health*, 23: 187–192. PMID:9243728
- Rando RJ, Shi R, Hughes JM *et al.* (2001). Cohort mortality study of North American industrial sand workers. III. Estimation of past and present exposures to respirable crystalline silica. *Ann Occup Hyg*, 45: 209–216. PMID:11295144

Silica dust, crystalline (quartz or cristobalite)

- Rappaport SM, Goldberg M, Susi P, Herrick RF (2003). Excessive exposure to silica in the US construction industry. *Ann Occup Hyg*, 47: 111–122. doi:10.1093/annhyg/meg025 PMID:12581996
- Reid PJ & Sluis-Cremer GK (1996). Mortality of white South African gold miners. *Occup Environ Med*, 53: 11–16. doi:10.1136/oem.53.1.11 PMID:8563852
- Renne RA, Eldridge SR, Lewis TR, Stevens DL (1985). Fibrogenic potential of intratracheally instilled quartz, ferric oxide, fibrous glass, and hydrated alumina in hamsters. *Toxicol Pathol*, 13: 306–314. doi:10.1177/019262338501300407 PMID:3010436
- Rice FL, Park R, Stayner L *et al.* (2001). Crystalline silica exposure and lung cancer mortality in diatomaceous earth industry workers: a quantitative risk assessment. *Occup Environ Med*, 58: 38–45. doi:10.1136/oem.58.1.38 PMID:11119633
- Saffiotti U (1990). *Lung cancer induction by silica in rats, but not in mice and hamsters: species differences in epithelial and granulomatous reactions*. In: *Environmental Hygiene II*. Seemayer NH, Hadnagy W, editors. New York: Springer Verlag, pp. 235–238. ISBN:0387527354.
- Saffiotti U (1992). *Lung cancer induction by crystalline silica*. In: *Relevance of Animal Studies to the Evaluation of Human Cancer Risk*. D'Amato R, Slaga TJ, Farland WH, Henry C, editors. New York: Wiley-Liss, pp. 51–69. ISBN:0471561835.
- Saffiotti U & Ahmed N (1995). Neoplastic transformation by quartz in the BALB/3T3/A31-1-1 cell line and the effects of associated minerals. *Teratog Carcinog Mutagen*, 15: 339–356. doi:10.1002/tcm.1770150609 PMID:8732883
- Saffiotti U, Williams AG, Daniel LN *et al.* (1996). *Carcinogenesis by crystalline silica: animal, cellular, and molecular studies*. In: *Silica and Silica-induced Lung Diseases*. Castranova V, Vallyathan V, Wallace WE, editors. Boca Raton: CRC Press, pp. 345–381. ISBN:0849347092.
- Sanderson WT, Steenland K, Daddens JA (2000). Historical respirable quartz exposures of industrial sand workers: 1946–1996. *Am J Ind Med*, 38: 389–398. doi:10.1002/1097-0274(200010)38:4<389::AID-AJIM4>3.0.CO;2-J PMID:10982979
- Sato M, Shames DS, Gazdar AF, Minna JD (2007). A translational view of the molecular pathogenesis of lung cancer. *J Thorac Oncol*, 2: 327–343. doi:10.1097/01.JTO.0000263718.69320.4c PMID:17409807
- Scarselli A, Binazzi A, Marinaccio A (2008). Occupational exposure to crystalline silica: estimating the number of workers potentially at high risk in Italy. *Am J Ind Med*, 51: 941–949. doi:10.1002/ajim.20619 PMID:18651580
- Schins RP (2002). Mechanisms of genotoxicity of particles and fibers. *Inhal Toxicol*, 14: 57–78. doi:10.1080/089583701753338631 PMID:12122560
- Schins RP, Duffin R, Höhr D *et al.* (2002a). Surface modification of quartz inhibits toxicity, particle uptake, and oxidative DNA damage in human lung epithelial cells. *Chem Res Toxicol*, 15: 1166–1173. doi:10.1021/tx025558u PMID:12230410
- Schins RP, Knaapen AM, Cakmak GD *et al.* (2002b). Oxidant-induced DNA damage by quartz in alveolar epithelial cells. *Mutat Res*, 517: 77–86. PMID:12034310
- Seiler F, Rehn B, Rehn S, Bruch J (2004). Different toxic, fibrogenic and mutagenic effects of four commercial quartz flours in the rat lung. *Int J Hyg Environ Health*, 207: 115–124. doi:10.1078/1438-4639-00275 PMID:15031954
- Shih T-S, Lu P-Y, Chen C-H *et al.* (2008). Exposure profiles and source identifications for workers exposed to crystalline silica during a municipal waste incinerator relining period. *J Hazard Mater*, 154: 469–475. doi:10.1016/j.jhazmat.2007.10.047 PMID:18063296
- Shimkin MB & Leiter J (1940). Induced pulmonary tumors in mice. III. The role of chronic irritation in the production of pulmonary tumors in strain A mice. *J Natl Cancer Inst*, 1: 241–254.
- Smith AH, Lopipero PA, Barroga VR (1995). Meta-analysis of studies of lung cancer among silicotics. *Epidemiology*, 6: 617–624. doi:10.1097/00001648-199511000-00010 PMID:8589094
- Spiethoff A, Wesch H, Wegener K, Klimisch H-J (1992). The effects of Thorotrast and quartz on the induction of lung tumors in rats. *Health Phys*, 63: 101–110. doi:10.1097/00004032-199207000-00011 PMID:1325960
- Steenland K (2005). One agent, many diseases: exposure–response data and comparative risks of different outcomes following silica exposure. *Am J Ind Med*, 48: 16–23. doi:10.1002/ajim.20181 PMID:15940719
- Steenland K & Brown D (1995). Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of follow-up. *Am J Ind Med*, 27: 217–229. doi:10.1002/ajim.4700270207 PMID:7755012
- Steenland K & Goldsmith DF (1995). Silica exposure and autoimmune diseases. *Am J Ind Med*, 28: 603–608. doi:10.1002/ajim.4700280505 PMID:8561170
- Steenland K & Greenland S (2004). Monte Carlo sensitivity analysis and Bayesian analysis of smoking as an unmeasured confounder in a study of silica and lung cancer. *Am J Epidemiol*, 160: 384–392. doi:10.1093/aje/kwh211 PMID:15286024
- Steenland K, 't Mannetje A, Boffetta P *et al.* International Agency for Research on Cancer. (2001). Pooled exposure–response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes Control*, 12: 773–784. doi:10.1023/A:1012214102061 PMID:11714104
- Steenland K & Sanderson W (2001). Lung cancer among industrial sand workers exposed to crystalline silica. *Am J Epidemiol*, 153: 695–703. doi:10.1093/aje/153.7.695 PMID:11282798

IARC MONOGRAPHS – 100C

- Steenland K & Stayner L (1997). Silica, asbestos, man-made mineral fibers, and cancer. *Cancer Causes Control*, 8: 491–503. doi:10.1023/A:1018469607938 PMID:9498906
- Stewart AP & Rice C (1990). A source of exposure data for occupational epidemiology studies. *Appl Occup Environ Hyg*, 5: 359–363.
- Stratta P, Canavese C, Messuerotti A *et al.* (2001). Silica and renal diseases: no longer a problem in the 21st century? *J Nephrol*, 14: 228–247. PMID:11506245
- ‘t Mannetje A, Steenland K, Checkoway H *et al.* (2002). Development of quantitative exposure data for a pooled exposure–response analysis of 10 silica cohorts. *Am J Ind Med*, 42: 73–86. doi:10.1002/ajim.10097 PMID:12125083
- Thibodeau MS, Giardina C, Knecht DA *et al.* (2004). Silica-induced apoptosis in mouse alveolar macrophages is initiated by lysosomal enzyme activity. *Toxicol Sci*, 80: 34–48. doi:10.1093/toxsci/kfh121 PMID:15056807
- Tjoe-Nij E, de Meer G, Smit J, Heederik D (2003). Lung function decrease in relation to pneumoconiosis and exposure to quartz-containing dust in construction workers. *Am J Ind Med*, 43: 574–583. doi:10.1002/ajim.10229 PMID:12768607
- Tse LA, Li ZM, Wong TW *et al.* (2007). High prevalence of accelerated silicosis among gold miners in Jiangxi, China. *Am J Ind Med*, 50: 876–880. doi:10.1002/ajim.20510 PMID:17948247
- Tsuda T, Babazono A, Yamamoto E *et al.* (1997). A Meta-Analysis on the Relationship between Pneumoconiosis and Lung Cancer. *J Occup Health*, 39: 285–294. doi:10.1539/joh.39.285
- Ulm K, Waschulzik B, Ehnes H *et al.* (1999). Silica dust and lung cancer in the German stone, quarrying, and ceramics industries: results of a case–control study. *Thorax*, 54: 347–351. doi:10.1136/thx.54.4.347 PMID:10092697
- Vallyathan V, Castranova V, Pack D *et al.* (1995). Freshly fractured quartz inhalation leads to enhanced lung injury and inflammation. Potential role of free radicals. *Am J Respir Crit Care Med*, 152: 1003–1009. PMID:7663775
- Verma DK, Kurtz LA, Sahai D, Finkelstein MM (2003). Current chemical exposures among Ontario construction workers. *Appl Occup Environ Hyg*, 18: 1031–1047. PMID:14612300
- Wagner JC (1970). *The pathogenesis of tumors following the intrapleural injection of asbestos and silica*. In: *Morphology of Experimental Respiratory Carcinogenesis*. Nettekheim P, Hanna MJ, Deatherage JW, editors. Oak Ridge, TN: US Atomic Energy Commission, pp. 347–358.
- Wagner JC & Berry G (1969). Mesotheliomas in rats following inoculation with asbestos. *Br J Cancer*, 23: 567–581. PMID:5360333
- Wagner MF & Wagner JC (1972). Lymphomas in the Wistar rat after intrapleural inoculation of silica. *J Natl Cancer Inst*, 49: 81–91. PMID:4338782
- Wagner MM (1976). Pathogenesis of malignant histiocytic lymphoma induced by silica in a colony of specificpathogen-free Wistar rats. *J Natl Cancer Inst*, 57: 509–518. PMID:185399
- Wagner MM, Wagner JC, Davies R, Griffiths DM (1980). Silica-induced malignant histiocytic lymphoma: incidence linked with strain of rat and type of silica. *Br J Cancer*, 41: 908–917. PMID:6252921
- Warheit DB, Webb TR, Colvin VL *et al.* (2007). Pulmonary bioassay studies with nanoscale and fine-quartz particles in rats: toxicity is not dependent upon particle size but on surface characteristics. *Toxicol Sci*, 95: 270–280. doi:10.1093/toxsci/kfl128 PMID:17030555
- Watkins DK, Chiazze L Jr, Fryar CD, Fayerweather W (2002). A case–control study of lung cancer and non-malignant respiratory disease among employees in asphaltroofingmanufacturingand asphaltproduction. *J Occup Environ Med*, 44: 551–558. doi:10.1097/00043764-200206000-00018 PMID:12085482
- Weeks JL & Rose C (2006). Metal and non-metal miners’ exposure to crystalline silica, 1998–2002. *Am J Ind Med*, 49: 523–534. doi:10.1002/ajim.20323 PMID:16691611
- Wernli KJ, Fitzgibbons ED, Ray RM *et al.* (2006). Occupational risk factors for esophageal and stomach cancers among female textile workers in Shanghai, China. *Am J Epidemiol*, 163: 717–725. doi:10.1093/aje/kwj091 PMID:16467414
- WHO (2000). *Concise International Chemical Assessment Document No. 24: Crystalline Silica, Quartz*. World Health Organization, Geneva.
- Wickman AR & Middendorf PJ (2002). An evaluation of compliance with occupational exposure limits for crystalline silica (quartz) in ten Georgia granite sheds. *Appl Occup Environ Hyg*, 17: 424–429. doi:10.1080/10473220290035444 PMID:12049432
- Wiencke JK, Thurston SW, Kelsey KT *et al.* (1999). Early age at smoking initiation and tobacco carcinogen DNA damage in the lung. *J Natl Cancer Inst*, 91: 614–619. doi:10.1093/jnci/91.7.614 PMID:10203280
- Wilson T, Scheuchenzuber WJ, Eskew ML, Zarkower A (1986). Comparative pathological aspects of chronic olivine and silica inhalation in mice. *Environ Res*, 39: 331–344. doi:10.1016/S0013-9351(86)80059-7 PMID:3007105
- Woskie SR, Kalil A, Bello D, Abbas Virji M (2002). Exposures to quartz, diesel, dust, and welding fumes during heavy and highway construction. *AIHAJ*, 63: 447–457. PMID:12486778.
- Xu Z, Brown LM, Pan GW *et al.* (1996). Cancer risks among iron and steel workers in Anshan, China, Part II: Case–control studies of lung and stomach cancer. *Am J Ind Med*, 30: 7–15.

Silica dust, crystalline (quartz or cristobalite)

- doi:10.1002/(SICI)1097-0274(199607)30:1<7::AID-AJIM2>3.0.CO;2-# PMID:8837676
- Yassin A, Yebesi F, Tingle R (2005). Occupational exposure to crystalline silica dust in the United States, 1988–2003. *Environ Health Perspect*, 113: 255–260. doi:10.1289/ehp.7384 PMID:15743711
- Yingratanasuk T, Seixas N, Barnhart S, Brodtkin D (2002). Respiratory health and silica exposure of stone carvers in Thailand. *Int J Occup Environ Health*, 8: 301–308. PMID:12412846
- Yu IT & Tse LA (2007). Exploring the joint effects of silicosis and smoking on lung cancer risks. *Int J Cancer*, 120: 133–139. doi:10.1002/ijc.22133 PMID:17036327
- Yu IT, Tse LA, Leung CC *et al.* (2007). Lung cancer mortality among silicotic workers in Hong Kong—no evidence for a link. *Ann Oncol*, 18: 1056–1063. doi:10.1093/annonc/mdm089 PMID:17586750
- Yucesoy B & Luster MI (2007). Genetic susceptibility in pneumoconiosis. *Toxicol Lett*, 168: 249–254. doi:10.1016/j.toxlet.2006.10.021 PMID:17161563
- Yucesoy B, Vallyathan V, Landsittel DP *et al.* (2002). Cytokine polymorphisms in silicosis and other pneumoconioses. *Mol Cell Biochem*, 234–235: 219–224. doi:10.1023/A:1015987007360 PMID:12162437
- Zhuang Z, Hearl FJ, Odencrantz J *et al.* (2001). Estimating historical respirable crystalline silica exposures for Chinese pottery workers and iron/copper, tin, and tungsten miners. *Ann Occup Hyg*, 45: 631–642. PMID:11718659
- Ziemann C, Jackson P, Brown R *et al.* (2009). Quartz-Containing Ceramic Dusts: *In vitro* screening of the cytotoxic, genotoxic and pro-inflammatory potential of 5 factory samples. *J Phys: Conf Ser*, 151: 1–6. doi:10.1088/1742-6596/151/1/012022

Exhibit J

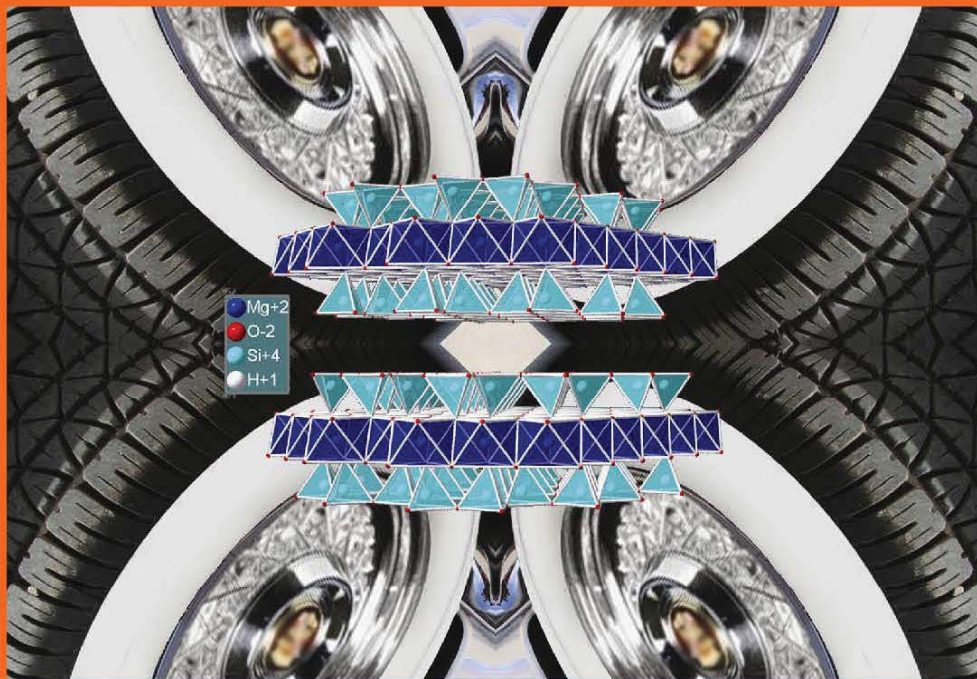
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WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



***IARC Monographs on the Evaluation of
Carcinogenic Risks to Humans***

VOLUME 93

**Carbon Black, Titanium Dioxide,
and Talc**

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

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IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at <http://monographs.iarc.fr/>.

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doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) **The Working Group** is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. **Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.**

(b) Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers

analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Tomiolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group

considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single

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species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) *Mechanistic and other relevant data*

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as ‘weak’, ‘moderate’ or ‘strong’. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of

biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans*.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of

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carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans*.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans*.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

5. Summary of Data Reported

5.1 Exposure data

The term 'talc' refers to both mineral talc and industrial mineral products that contain mineral talc in proportions that range from about 35% to almost 100% and are marketed under the name talc. Mineral talc occurs naturally in many regions of the world where metamorphosed mafic and ultramafic rocks or magnesium carbonates occur. Mineral talc is usually platy but may also occur as asbestiform fibres. (Asbestiform refers to a habit (pattern) of mineral growth and not to the presence of other minerals. Asbestiform talc must not be confused with talc that contains asbestos.) Together with platy talc, asbestiform talc is found in the Gouverneur District of New York State, USA, and occasionally elsewhere; it may be associated with other minerals as observed by transmission electron microscopy.

Talc products vary in their particle size, associated minerals and talc content depending on their source and application. Minerals commonly found in talc products include chlorite and carbonate. Less commonly, talc products contain tremolite, anthophyllite and serpentine.

Mineral talc is valued for its softness, platyness, inertness and ability to absorb organic matter. It is used in agricultural products, ceramics, paint and other coatings, paper, plastics, roofing, rubber, cosmetics and pharmaceuticals and for waste treatment. Cosmetic talc, which contains more than 90% mineral talc, is present in many cosmetic products and is used for many purposes, including baby powders and feminine hygiene products. The type of talc that is currently used for cosmetic purposes in the USA does not contain detectable levels of amphibole, including asbestos. It is not known whether this is true in other countries.

Workers are exposed to talc during its mining and milling. Reported geometric mean exposure levels to respirable dust are typically in the range of 1–5 mg/m³. Workers may also be exposed in user industries, primarily in the rubber, pulp and paper and ceramics industries. Due to the presence of other particulates, exposure levels may be difficult to measure accurately. Consumer exposure by inhalation could occur during the use of loose powders that contain talc.

Accurate estimates of prevalence are not available. However, in some series of controls from epidemiological studies of ovarian cancer, the prevalence of use for feminine hygiene of body powders, baby powders, talcum powders and deodorizing powders, most of which contain cosmetic talc in varying amounts, has been reported to be as high as 50% in some countries. Perineal use for such purposes seems to have been a common practice in Australia, Canada, the United Kingdom, the USA and other countries, including Pakistan. Use of cosmetic talc in the USA has declined steadily since the late 1970s.

5.2 Human carcinogenicity data

The carcinogenic effect of exposure to talc not contaminated by asbestos fibres has been investigated in five independent but relatively small cohort studies of talc miners and millers in Austria, France, Italy, Norway and the USA. The miners and to a lesser extent the millers in these cohorts were also exposed to quartz. In a case-control study nested in the combined cohorts of talc workers from Austria and France, there was no tendency of higher risks for lung cancer by increasing cumulative exposure of workers to talc dust. In four of five studies, it was explicitly stated that no case of mesothelioma was observed. In the two studies from Italy and Norway, which included an estimate of cumulative exposure of the cohort to talc dust, the risk for lung cancer in the highest category was found to be close to or below unity. In the subgroup of miners in the study in the USA, an excess risk for lung cancer was found, which may have been due to exposure in the workplace to radon daughters and quartz. In all the other groups of workers studied, there was no increased risk for lung cancer.

Female workers in the Norwegian pulp and paper industry had an increased risk for ovarian cancer, which, however, was attributed to exposure to asbestos. A community-based case-control study did not find an increased risk for ovarian cancer associated with occupational exposure to talc, but the prevalence of exposure was low.

Body powder containing talc has been used by women on the perineum (or genital area), on sanitary napkins and on diaphragms. In total, data from one prospective cohort study and 19 case-control studies were reviewed in the evaluation of the association of cosmetic talc use and the risk for ovarian cancer. The information collected on perineal talc use varied substantially by study (e.g. ever use versus regular use, and whether information on the mode of application, frequency or duration of use was available).

The cohort study was conducted among nurses in the USA and included 307 cases of ovarian cancer that occurred over 900 000 person-years of observation and a maximum of 14 years of follow-up. Information was collected on the frequency but not duration of regular use. Perineal use of talc was not associated with a risk for ovarian cancer.

The 20 case-control studies were conducted in Australia, Canada, China, Greece, Israel, Norway, the United Kingdom and the USA (nested case-control study), and included between 77 and 824 cases and 46 and 1367 controls. Five were hospital-based designs and the others were population-based studies. The Working Group designated a subset of these studies as being more informative based on the following characteristics: the study was population-based, was of a reasonable size, had acceptable participation rates and included information to allow control for potentially important confounders.

Eight population-based case-control studies from Australia, Canada (Ontario) and the USA (two non-overlapping studies in Boston, MA, and one each in California, Delaware Valley, eastern Massachusetts and New Hampshire and Washington State) were thereby identified as being more informative. The selected studies included at least 188 cases and had participation rates that generally ranged from 60 to 75%. Among these eight studies, the prevalence of use of body powder among controls ranged from 16 to 52%; however,

information on exposure was not collected in a comparable manner across studies. In addition, the frequency and duration of use or total lifetime applications were investigated in several studies as well as consideration of prior tubal ligation or simple hysterectomy. Only sparse data were available on whether women had used body powder before or after the mid-1970s.

The relative risks for ovarian cancer among users of body powder (versus non-users) were homogenous across this relatively diverse set of eight studies, each of which indicated a 30–60% increase in risk. Among the other 11 case–control studies, most also reported relative risks of this magnitude or higher. The subset of studies that assessed use of talc on a diaphragm were relatively uninformative due to their lack of precision.

Results on exposure–response relationships were presented in the cohort study and in seven of the more informative case–control studies. In the cohort study, no exposure–response trend was apparent. Positive exposure–response trends were apparent in the two Boston-based studies that presented the most comprehensive analysis. In the Canadian and Californian studies, a non-significant, weakly positive trend was observed for either duration or frequency of use, but not for both. In the other three case–control studies, no consistent trend was observed and the strongest associations tended to be seen among the shorter-term or less frequent talc users.

The cohort study and four of the eight more informative case–control studies presented results on histological type of ovarian cancer. When the analysis of the cohort study was restricted to the 160 serous invasive cases, a statistically significant increase in risk of about 40% was observed. The risk increased with increasing frequency of body powder use. Risks for serous ovarian cancer were somewhat greater than those for other histological types in two of the four case–control studies in which the contrast was reported. Results for other histological types were inconclusive.

The Working Group carefully weighed the various limitations and biases that could have influenced these findings. Non-differential misclassification of talc use, given the relatively crude definitions available, would have attenuated any true association. Although the available information on potential confounders varied by study, most investigators accounted for age, oral contraceptive use and parity. In most studies, only the adjusted relative risks were presented; however, in the three studies in which both age-adjusted and fully adjusted estimates were provided, relative risks did not differ materially, suggesting minimal residual confounding.

It is possible that confounding by unrecognized risk factors may have distorted the results. One or more such factors, if they are causes of ovarian cancer and also associated in the population with perineal use of talc, could induce the appearance of an association between the use of talc and ovarian cancer where there is none. In order for such an unrecognized risk factor to induce the consistent pattern of excess risks in all of the case–control studies, it would be necessary for the factor to be associated with perineal talc use across different countries and different decades. While the range of countries and decades covered by the more informative case–control studies is not very broad, it provides some

diversity of social and cultural context and thereby reduces the likelihood of a hidden confounder.

There was a distinct pattern of excess risk discernible in all of the case-control studies when users were compared with non-users; however, methodological factors needed to be considered. First, while chance cannot be ruled out as an explanation, it seemed very unlikely to be responsible for the consistent pattern of excess risks. A second possible explanation would be recall bias, to which case-control studies may be particularly susceptible. This may have been the case if there had been widespread publicity about the possible association between the use of body powder and cancer. In such circumstances, it is possible that women who had ovarian cancer could be more likely than women who did not to remember or over-report a habit, such as body powder use, if they thought that it may have played a role in their illness. There was a flurry of publicity in the USA in the mid-1970s concerning the possible risks for cancer posed by the use of talc-based body powders. Following an industry decision to market talc powders with no asbestos, it was the opinion of the Working Group that there had not been widespread public concern about this issue, at least until very recently. Therefore, the Working Group considered it unlikely that such a bias could explain the set of consistent findings that stretch over two decades. The Working Group believed that recall bias was a possibility inherent in the case-control studies and could not be ruled out. The Working Group also considered publication and selection biases and these were not judged to have substantially influenced the pattern of findings.

The Working Group searched for documentation on the presence of known hazardous minerals in talc-based body powders. There were strong indications that these products contained quartz in the mid-1970s and still do. There were also indications that occasional small concentrations of asbestos were present in these products before the mid-1970s, but the available information was sparse, sampling methods and detection limits were not described, and the range of locations where data were available was extremely limited. As a result, the Working Group found it difficult to identify a date before which talc-based body powders contained other hazardous minerals and after which they did not, or to have confidence that this would be applicable worldwide. In addition, the epidemiological studies generally do not provide information about the years during which the female subjects were exposed. Consequently, the Working Group could not identify studies in which an uncontaminated form of talc was the only one used by study subjects. Nevertheless, the Working Group noted that, even in the most recent studies in the USA, where exposure histories may have been much less affected by hazardous contaminants of talc, the risk estimates were not different from the early studies in which the possibility of such exposure was more likely.

To evaluate the evidence on whether perineal use of talc causes an increased risk for ovarian cancer, the Working Group noted the following:

- The eight more informative case-control studies, as well as most of the less informative ones, provided overall estimates of excess risk that were remarkably consistent; seven of these eight case-control studies examined exposure-response

relationships; two provided evidence supporting such a relationship, two provided mixed evidence and three did not support an association.

- The cohort study neither supports nor strongly refutes the evidence from the case-control studies.
- Case-control studies were susceptible to recall bias which could tend to inflate risk estimates but to an unknown degree.
- All of the studies were susceptible to other potential biases which could either increase or decrease the association.
- All of the studies involved some degree of non-differential misclassification of exposure that would tend to underestimate any true underlying association.

5.3 Animal carcinogenicity data

Talc of different grades was tested for carcinogenicity in mice by inhalation exposure, intrathoracic, intraperitoneal and subcutaneous injection, in rats by inhalation exposure, intrathoracic injection, intraperitoneal injection, oral administration and intrapleural and ovarian implantation, and in hamsters by inhalation exposure and intratracheal injection.

In male and female rats exposed by inhalation to a well-defined talc, the incidence of alveolar/bronchiolar carcinoma or adenoma and carcinoma (combined) was significantly increased in female rats. The incidence of adrenal medulla pheochromocytomas (benign, malignant or complex (combined)) showed a significant positive trend and the incidence in high-dose males and females was significantly greater than that in controls. The incidence of malignant pheochromocytomas was also increased in high-dose females. The Working Group did not consider it probable that the increased incidence of pheochromocytomas was causally related to talc but, based on the experimental data available, neither could talc-related effects be excluded.

Tumour incidence was not increased following the intrapleural or intrathoracic administration of a single dose of various talcs to rats. In two studies of intraperitoneal administration in rats, no increase in the incidence of mesotheliomas was observed. No increased incidence of tumours was produced in rats in two studies of talc administered in the diet or in another study of the implantation of talc on to the ovary.

Tumour incidence was not increased in mice following the inhalation of talc in one study, the intrathoracic administration of a single dose of various talcs in another study or the administration of talc by intraperitoneal injections in three studies. A single subcutaneous injection of talc into mice did not produce local tumours.

Tumour incidence was not increased following inhalation or intratracheal administration of talc to hamsters.

5.4 Mechanistic considerations and other relevant data

Different mechanisms are probably operative in the effects of talc on the lung and pleura, depending on the route of exposure.

In humans, deposition, retention and clearance of talc have been insufficiently studied, although talc particles have been found at autopsy in the lungs of talc workers.

In humans and experimental animals, the effects of talc are dependent on the route of exposure, and the dose and properties of the talc. Talc pneumoconiosis was somewhat more prevalent and severe among miners exposed to talc containing asbestiform minerals and/or asbestos than among those exposed to talc without such contaminants. However, the role of quartz and asbestos in the observed pneumoconiosis could not be ruled out. Among drug users, intravenous injection of talc present as a filler in the drugs resulted in microembolization in a variety of organs and alterations in pulmonary function.

In animal studies, talc has been shown to cause granulomas and mild inflammation when inhaled. Observations of the effects that occurred in the lungs of rats exposed by inhalation to talc suggested that the operative mechanisms may be similar to those identified for carbon black, and talc is known to cause the release of cytokines, chemokines and growth factors from pleural mesothelial cells.

In humans, intrapleural administration of talc as a therapeutic procedure results in pleural inflammation which leads to pleural fibrosis and symphysis. Pleural fibrosis is the intended effect of intrapleural administration of talc in patients with malignant pleural effusions or pneumothorax. Animal studies suggested that extrapulmonary transport of talc following pleurodesis increases with decreasing particle size and increasing administered dose. Talc has been shown to cause apoptosis of malignant cells *in vitro*.

Perineal exposure to cosmetic talc in women is of concern because of its possible association with ovarian cancer. Several studies have been conducted in women to assess potential retrograde movement of particles through the reproductive tract to the ovaries. These have been conducted in women who were about to undergo gynaecological surgery, most of whom had diseases or complications of the reproductive tract and organs that required surgery. The findings reported in these studies may be confounded by the various levels of dysfunction in clearance from the female reproductive tract due to underlying pathologies. In addition, most of the studies had little or no further information on the use of talc products for perineal hygiene or changes in habits that may have preceded surgery. On balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak. In women with impaired clearance function, some evidence of retrograde transport was found. Studies in animals (rodents, langomorphs and non-human primates) showed no evidence of retrograde transport of talc to the ovaries.

In one study, predictors of the presence of antibodies to mucin protein were inversely related to the risk for ovarian cancer and exposure to powder containing talc.

No data were available on the genotoxic effects of exposure to talc in humans. The limited number of studies available on the genetic toxicology of talc *in vitro* gave negative results.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres.

There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres.

6.3 Overall evaluation

Perineal use of talc-based body powder is *possibly carcinogenic to humans* (Group 2B).

Inhaled talc not containing asbestos or asbestiform fibres is *not classifiable as to its carcinogenicity* (Group 3).

6.4 Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as evidence regarding the potential mechanisms through which talc might cause cancer in humans.

The Working Group found little or inconsistent evidence of an increased risk for cancer in the studies of workers occupationally exposed to talc. The studies of talc miners and millers were considered to provide the best source of evidence, but no consistent pattern was seen. One study observed an excess risk for lung cancer among miners, but confounding from exposure to other carcinogens made it difficult to attribute this to talc and no excess risk was seen in millers. Other studies also found no increased cancer risk or no higher risk with increasing cumulative exposure. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether inhaled talc not containing asbestos or asbestiform fibres causes cancer in humans.

For perineal use of talc-based body powder, many case-control studies of ovarian cancer found a modest, but unusually consistent, excess in risk, although the impact of bias and potential confounding could not be ruled out. In addition, the evidence regarding exposure-response was inconsistent and the one cohort study did not provide support for an association between talc use and ovarian cancer. Concern was also expressed that

exposure was defined in a variety of ways and that some substances called talc may have contained quartz and other potentially carcinogenic materials. A small number of Working Group members considered the evidence to be inadequate. Despite these reservations, the Working Group concluded that the epidemiological studies taken together provide *limited evidence* of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer.

In one study of rats that inhaled talc, an excess incidence of malignant lung tumours was seen in females. The same study observed an excess incidence of pheochromocytomas in the adrenal medulla in both sexes, but the Working Group was divided as to whether these rare tumours could be attributed to exposure to talc. Other studies in rats and mice using different routes of administration did not find an excess of cancer, and two studies in rats were considered to be inadequate for evaluation. Based on the one positive study, the Working Group found that there was *limited evidence* of carcinogenicity of inhaled talc in experimental animals. There was no agreement within the Working Group as to whether the evidence on pheochromocytomas should be taken into account in the evaluation of animal data.

Exhibit K

Meeting January 14 1965

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(Professor Emeritus of Medical Statistics,
University of London)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized?

There are, of course, instances in which we can reasonably answer these questions from the general body of medical knowledge. A particular, and perhaps extreme, physical environment cannot fail to be harmful; a particular chemical is known to be toxic to man and therefore suspect on the factory floor. Sometimes, alternatively, we may be able to consider what *might* a particular environment do to man, and then see whether such consequences are indeed to be found. But more often than not we have no such guidance, no such means of proceeding; more often than not we are dependent upon our observation and enumeration of defined events for which we then seek antecedents. In other words we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this

President's Address

observed *association* to a verdict of *causation*?
Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) *Strength*. First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the *enormous* increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'

To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times

as great. On the other hand the death rate from coronary thrombosis in smokers is no more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand-in-hand with smoking – features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic ‘you can’t prove it, there *may* be such a feature’.

Certainly in this situation I would reject the argument sometimes advanced that what matters is the absolute difference between the death rates of our various groups and not the ratio of one to other. That depends upon what we want to know. If we want to know how many extra deaths from cancer of the lung will take place through smoking (i.e. presuming causation), then obviously we must use the absolute differences between the death rates – 0.07 per 1,000 per year in non-smoking doctors, 0.57 in those smoking 1–14 cigarettes daily, 1.39 for 15–24 cigarettes daily and 2.27 for 25 or more daily. But it does not follow here, or in more specifically occupational problems, that this best measure of the effect upon mortality is also the best measure in relation to aetiology. In this respect the ratios of 8, 20 and 32 to 1 are far more informative. It does not, of course, follow that the differences revealed by ratios are of any practical importance. Maybe they are, maybe they are not; but that is another point altogether.

We may recall John Snow’s classic analysis of the opening weeks of the cholera epidemic of 1854 (Snow 1855). The death rate that he recorded in the customers supplied with the grossly polluted water of the Southwark and Vauxhall Company was in truth quite low – 71 deaths in each 10,000 houses. What stands out vividly is the fact that the small rate is 14 times the figure of 5 deaths per 10,000 houses supplied with the sewage-free water of the rival Lambeth Company.

In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on

the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so. Relatively few persons harbouring the meningococcus fall sick of meningococcal meningitis. Relatively few persons occupationally exposed to rat’s urine contract Weil’s disease.

(2) *Consistency*: Next on my list of features to be specially considered I would place the *consistency* of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

This requirement may be of special importance for those rare hazards singled out in the Section’s terms of reference. With many alert minds at work in industry today many an environmental association may be thrown up. Some of them on the customary tests of statistical significance will appear to be unlikely to be due to chance. Nevertheless whether chance is the explanation or whether a true hazard has been revealed may sometimes be answered only by a repetition of the circumstances and the observations.

Returning to my more general example, the Advisory Committee to the Surgeon-General of the United States Public Health Service found the association of smoking with cancer of the lung in 29 retrospective and 7 prospective inquiries (US Department of Health, Education & Welfare 1964). The lesson here is that broadly the same answer has been reached in quite a wide variety of situations and techniques. In other words we can justifiably infer that the association is not due to some constant error or fallacy that permeates every inquiry. And we have indeed to be on our guard against that.

Take, for instance, an example given by Heady (1958). Patients admitted to hospital for operation for peptic ulcer are questioned about recent domestic anxieties or crises that may have precipitated the acute illness. As controls, patients admitted for operation for a simple hernia are similarly quizzed. But, as Heady points out, the two groups may not be *in pari materia*. If your wife ran off with the lodger last week you still have to take your perforated ulcer to hospital without delay. But with a hernia you might prefer to stay at home for a while – to mourn (or celebrate) the event. No number of exact repetitions would remove or necessarily reveal that fallacy.

We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the

original evidence; yet the same results from precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would myself put a good deal of weight upon similar results reached in quite different ways, e.g. prospectively and retrospectively.

Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions. The experience of the nickel refiners of South Wales is an outstanding example. I quote from the Alfred Watson Memorial Lecture that I gave in 1962 to the Institute of Actuaries:

'The population at risk, workers and pensioners, numbered about one thousand. During the ten years 1929 to 1938, sixteen of them had died from cancer of the lung, eleven of them had died from cancer of the nasal sinuses. At the age specific death rates of England and Wales at that time, one might have anticipated one death from cancer of the lung (to compare with the 16), and a fraction of a death from cancer of the nose (to compare with the 11). In all other bodily sites cancer had appeared on the death certificate 11 times and one would have expected it to do so 10-11 times. There had been 67 deaths from all other causes of mortality and over the ten years' period 72 would have been expected at the national death rates. Finally division of the population at risk in relation to their jobs showed that the excess of cancer of the lung and nose had fallen wholly upon the workers employed in the chemical processes.

'More recently my colleague, Dr Richard Doll, has brought this story a stage further. In the nine years 1948 to 1956 there had been, he found, 48 deaths from cancer of the lung and 13 deaths from cancer of the nose. He assessed the numbers expected at normal rates of mortality as, respectively 10 and 0.1.

'In 1923, long before any special hazard had been recognized, certain changes in the refinery took place. No case of cancer of the nose has been observed in any man who first entered the works after that year, and in these men there has been no excess of cancer of the lung. In other words, the excess in both sites is uniquely a feature in men who entered the refinery in, roughly, the first 23 years of the present century.

'No causal agent of these neoplasms has been identified. Until recently no animal experimentation had given any clue or any support to this wholly statistical evidence. Yet I wonder if any of us would hesitate to accept it as proof of a grave industrial hazard?' (Hill 1962).

In relation to my present discussion I know of no parallel investigation. We have (or certainly had) to make up our minds on a unique event; and there is no difficulty in doing so.

(3) *Specificity*: One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider. If, as here, the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation.

We must not, however, over-emphasize the importance of the characteristic. Even in my present example there is a cause and effect relationship with two different sites of cancer – the lung and the nose. Milk as a carrier of infection and, in that sense, the cause of disease can produce such a disparate galaxy as scarlet fever, diphtheria, tuberculosis, undulant fever, sore throat, dysentery and typhoid fever. Before the discovery of the underlying factor, the bacterial origin of disease, harm would have been done by pushing too firmly the need for specificity as a necessary feature before convicting the dairy.

Coming to modern times the prospective investigations of smoking and cancer of the lung have been criticized for not showing specificity – in other words the death rate of smokers is higher than the death rate of non-smokers from many causes of death (though in fact the results of Doll & Hill, 1964, do not show that). But here surely one must return to my first characteristic, the strength of the association. If other causes of death are raised 10, 20 or even 50% in smokers whereas cancer of the lung is raised 900-1,000% we have specificity – a specificity in the magnitude of the association.

We must also keep in mind that diseases may have more than one cause. It has always been possible to acquire a cancer of the scrotum without sweeping chimneys or taking to mule-spinning in Lancashire. One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answers we might get back to a single factor.

In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.

(4) *Temporality*: My fourth characteristic is the temporal relationship of the association – which is the cart and which the horse? This is a question which might be particularly relevant with diseases of slow development. Does a particular diet lead to disease or do the early stages of the disease lead to those peculiar dietetic habits? Does a

particular occupation or occupational environment promote infection by the tubercle bacillus or are the men and women who select that kind of work more liable to contract tuberculosis whatever the environment – or, indeed, have they already contracted it? This temporal problem may not arise often but it certainly needs to be remembered, particularly with selective factors at work in industry.

(5) *Biological gradient*: Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers. That comparison would be weakened, though not necessarily destroyed, if it depended upon, say, a much heavier death rate in light smokers and a lower rate in heavier smokers. We should then need to envisage some much more complex relationship to satisfy the cause-and-effect hypothesis. The clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light.

The same would clearly be true of an alleged dust hazard in industry. The dustier the environment the greater the incidence of disease we would expect to see. Often the difficulty is to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose-response. But we should invariably seek it.

(6) *Plausibility*: It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill 1962), there was

‘... no biological knowledge to support (or to refute) Pott’s observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other “absurd” associations, that “it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected”. And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella.’

In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr Watson, ‘when you have eliminated the impossible, whatever remains, however improbable, must be the truth.’

(7) *Coherence*: On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease – in the expression of the Advisory Committee to the Surgeon-General it should have coherence.

Thus in the discussion of lung cancer the Committee finds its association with cigarette smoking coherent with the temporal rise that has taken place in the two variables over the last generation and with the sex difference in mortality – features that might well apply in an occupational problem. The known urban/rural ratio of lung cancer mortality does not detract from coherence, nor the restriction of the effect to the lung.

Personally, I regard as greatly contributing to coherence the histopathological evidence from the bronchial epithelium of smokers and the isolation from cigarette smoke of factors carcinogenic for the skin of laboratory animals. Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiological observations in man. Arsenic can undoubtedly cause cancer of the skin in man but it has never been possible to demonstrate such an effect on any other animal. In a wider field John Snow’s epidemiological observations on the conveyance of cholera by the water from the Broad Street pump would have been put almost beyond dispute if Robert Koch had been then around to isolate the vibrio from the baby’s nappies, the well itself and the gentleman in delicate health from Brighton. Yet the fact that Koch’s work was to be awaited another thirty years did not really weaken the epidemiological case though it made it more difficult to establish against the criticisms of the day – both just and unjust.

(8) *Experiment*: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest

support for the causation hypothesis may be revealed.

(9) *Analogy*: In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy.

Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

Tests of Significance

No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis.

Nearly forty years ago, amongst the studies of occupational health that I made for the Industrial Health Research Board of the Medical Research Council was one that concerned the workers in the cotton-spinning mills of Lancashire (Hill 1930). The question that I had to answer, by the use of the National Health Insurance records of that time, was this: Do the workers in the cardroom of the spinning mill, who tend the machines that clean the raw cotton, have a sickness experience in any way different from that of other operatives in the same mills who are relatively unexposed to the dust and fibre that were features of the cardroom? The answer was an unqualified 'Yes'. From age 30 to age 60 the cardroom workers suffered over three times as much from respiratory causes of illness whereas from non-respiratory causes their experience was not different from that of the other workers. This pronounced difference with the respiratory causes was derived not from abnormally long periods of sickness but rather from an excessive number of repeated absences from work of the cardroom workers.

All this has rightly passed into the limbo of forgotten things. What interests me today is this: My results were set out for men and women separately and for half a dozen age groups in 36 tables. So there were plenty of sums. Yet I cannot find that anywhere I thought it necessary to use a test of significance. The evidence was so clear-cut, the differences between the groups were mainly so large, the contrast between respiratory and non-respiratory causes of illness so specific, that no formal tests could really contribute anything of value to the argument. So why use them?

Would we think or act that way today? I rather doubt it. Between the two world wars there was a strong case for emphasizing to the clinician and other research workers the importance of not overlooking the effects of the play of chance upon their data. Perhaps too often generalities were based upon two men and a laboratory dog while the treatment of choice was deduced from a difference between two bedfuls of patients and might easily have no true meaning. It was therefore a useful corrective for statisticians to stress, and to teach the need for, tests of significance merely to serve as guides to caution before drawing a conclusion, before inflating the particular to the general.

I wonder whether the pendulum has not swung too far – not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard errors can surely be just as silly? Fortunately I believe we have not yet gone so far as our friends in the USA where, I am told, some editors of journals will return an article because tests of significance have not been applied. Yet there are innumerable situations in which they are totally unnecessary – because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance. What is worse the glitter of the *t* table diverts attention from the inadequacies of the fare. Only a tithe, and an unknown tithe, of the factory personnel volunteer for some procedure or interview, 20% of patients treated in some particular way are lost to sight, 30% of a randomly-drawn sample are never contacted. The sample may, indeed, be akin to that of the man who, according to Swift, 'had a mind to sell his house and carried a piece of brick in his pocket, which he showed as a pattern to encourage purchasers'. The writer, the editor and the reader are unmoved. The magic formulæ are there.

Of course I exaggerate. Yet too often I suspect we waste a deal of time, we grasp the shadow and

lose the substance, we weaken our capacity to interpret data and to take reasonable decisions whatever the value of P . And far too often we deduce 'no difference' from 'no significant difference'. Like fire, the χ^2 test is an excellent servant and a bad master.

The Case for Action

Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it – or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually to take action. If this be operative cause and that be deleterious effect, then we shall wish to intervene to abolish or reduce death or disease.

While that is a commendable ambition it almost inevitably leads us to introduce differential standards before we convict. Thus on relatively slight evidence we might decide to restrict the use of a drug for early-morning sickness in pregnant women. If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive.

On fair evidence we might take action on what appears to be an occupational hazard, e.g. we might change from a probably carcinogenic oil

to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong. But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like. In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act.

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day.

REFERENCES

- Doll R (1964) In: *Medical Surveys and Clinical Trials*. Ed. L J Witts. 2nd ed. London; p 333
- Doll R & Hill A B (1964) *Brit. med. J.* i, 1399, 1460
- Heady J A (1958) *Med. World, Lond.* 89, 305
- Hill A B
(1930) *Sickness amongst Operatives in Lancashire Spinning Mills*. Industrial Health Research Board Report No. 59. HMSO, London
(1962) *J. Inst. Actu.* 88, 178
- Snow J (1855) *On the Mode of Communication of Cholera*. 2nd ed. London (Reprinted 1936, New York)
- US Department of Health, Education & Welfare (1964) *Smoking and Health*. Public Health Service Publication No. 1103. Washington

Exhibit L

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM
POWDER PRODUCTS MARKETING, SALES
PRACTICES AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**EXPERT REPORT OF CHRISTIAN MERLO, MD, MPH
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019



Christian Merlo, M.D., M.P.H.

I. SCOPE OF REPORT

I was asked to address fundamental tenets of epidemiology, to review the epidemiology related to the potential association between perineal talc use and ovarian cancer, to review plaintiffs' epidemiology experts' reports, and to offer my opinions on their methodologies.

All of the opinions in this report are stated to a reasonable degree of scientific certainty.

I am being compensated at a rate of \$530 per hour for record review and drafting my report and \$720 per hour for testimony.

My curriculum vitae, a list of literature that I have reviewed, and a list of testimony I have provided in the last four years may be found in Appendices A, B and C.

II. PROFESSIONAL QUALIFICATIONS

My name is Christian Merlo. I am a licensed physician in the state of Maryland and am board certified in internal medicine, pulmonary medicine and critical care medicine. I am an attending physician at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center and care for patients both in the hospital and in our outpatient centers. I am Associate Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the Johns Hopkins University School of Medicine, and in addition, I am Associate Professor of Epidemiology in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health. I am also a member of the *Alpha Omega Alpha* honor society for medicine.

I have provided patient care and consultation as a clinical physician and have taught medicine in the fields of general medicine, pulmonary medicine and critical care medicine for more than 18 years.

I received my doctorate in medicine at Georgetown University School of Medicine and completed my residency in internal medicine at Georgetown University Medical Center, where I also served as Chief Resident. I completed a four-year fellowship in Pulmonary and Critical Care Medicine at the Johns Hopkins Hospital, and during this period in time, I also received a master's degree in public health from the Johns Hopkins Bloomberg School of Public Health.

I was offered a faculty position in 2004 as Instructor in Medicine at the Johns Hopkins University School of Medicine, and was promoted to Assistant Professor of Medicine in 2006. In 2009, I was awarded a joint faculty appointment as Assistant Professor of Epidemiology at the Johns Hopkins Bloomberg School of Public Health, and in 2015, I was promoted to Associate Professor of Medicine and Epidemiology.

I am the Associate Program Director of the Adult Cystic Fibrosis Program at the Johns Hopkins Cystic Fibrosis Center, one of the largest cystic fibrosis centers in the country, and in addition, I am the Director of Research for both the Adult Cystic Fibrosis Program and the Lung Transplant Program at the Johns Hopkins Hospital. I am also an Associate Program Director for Research and Scholarship for the Osler Medical Residency

program. I have specific expertise in the clinical care of patients with cystic fibrosis and those who undergo lung transplantation, as well as in the care of patients with other pulmonary diseases or those that require critical care therapies. My research involves the design of clinical studies investigating the impact of environmental and infectious exposures on outcomes for patients with cystic fibrosis and those who undergo lung transplantation.

I am currently principal investigator or co-investigator on many NIH-funded and pharmaceutical industry-sponsored clinical trials. I have authored or co-authored more than 70 manuscripts, book chapters and commentaries on topics involving cystic fibrosis and lung transplantation, as well as on topics in general pulmonary medicine and critical care medicine. As a clinical investigator, I have had rigorous training and have expertise in clinical epidemiology, with specific training in clinical trial design, conduct and analysis. My ties with the School of Public Health have provided ongoing collaboration to help research the epidemiologic nature of the exposure/outcome causal pathway in diseases involving internal medicine, pulmonary medicine and critical care medicine.

I am also an expert in the methodologic approach to the study of disease and have more than 15 years of experience teaching coursework on study design and analysis, as well as conducting research on the epidemiologic nature of the exposure/outcome relationship with a strong command of the strengths and limitations of epidemiologic investigation.

III. FUNDAMENTAL PRINCIPLES OF EPIDEMIOLOGY

Although there are many definitions of epidemiology, a widely accepted definition describes epidemiology as:

*the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems.*¹

Epidemiology is a scientific discipline that relies heavily on an unbiased approach to the collection, analysis and interpretation of data. Epidemiology places an emphasis on the frequency and rate of health events as well as how personal characteristics such as demographics, socioeconomic status, behaviors and environmental exposures play a role in health-related events. Epidemiology is a science, and epidemiologic studies, when designed, conducted, analyzed and interpreted appropriately, can be powerful tools in the critical examination of the causal pathway between exposure and outcome.

A. Fundamentals Of Epidemiologic Study Design

Researchers often have to choose a study design based on the research question, as not all study designs are appropriate for all questions. Many research questions are suitable to be answered using a classic experimental design such as the randomized controlled trial. For instance, it may be appropriate to use a randomized controlled trial design to investigate

¹ See, e.g., Centers for Disease Control & Prevention, Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics, Lesson 1: Introduction to Epidemiology, <https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section1.html> (footnote omitted).

the effect of a new cholesterol lowering agent on mortality in patients with heart disease. An example of this is the Scandinavian Simvastatin Survival Study,² in which researchers studied 4,444 patients with heart disease who were either treated with simvastatin or placebo. The investigators found a significant reduction in the risk of death from heart disease in the simvastatin group compared to placebo.

Other research questions are not suitable for an experimental design in humans because of the potential for harm, lack of equipoise or ethical concerns. One such example is the effect of cigarette smoking on risk of death and risk of death from lung cancer. In order to attempt to answer this, researchers would not be able to use an experimental design, and more likely would have to use an observational study design. Doll and Hill³ sent out a short but detailed questionnaire asking more than 59,000 British physicians about smoking habits and obtained follow-up information regarding mortality and lung cancer risk. In this very large observation cohort, Doll and Hill were able to demonstrate a significant increase in all-cause mortality as well as deaths due to lung cancer among cigarette smokers when compared to non-smokers.

Sometimes, the experimental study design is appropriate, and other times, an observational study design is necessary, but it is only with careful and detailed attention to the study design (study type, study size, exposure assessment, attempt to limit bias and confounding), conduct and analysis that the cause of disease can possibly be determined.

B. Limitations Of Epidemiologic Study Design

All epidemiologic studies have the advantage and limitation of studying humans rather than experimental animals. Each epidemiologic study design (detailed in the **STUDY DESIGN CONSIDERATIONS** section), however, not only has its strengths, but also weaknesses.

For example, consider the design of an epidemiologic study to evaluate the question:

“Does regular aerobic exercise decrease the risk of heart disease?”

A randomized controlled trial, one might think, would be the most rigorous approach and the method most similar to a laboratory scientist working in a highly controlled environment with experimental animals. Suppose researchers choose a group of subjects who don't exercise regularly, divide the group randomly into an intervention group, who are instructed to perform aerobic exercise for 30 minutes three times a week, and a control group, who are instructed to continue with a low exercise lifestyle. The investigators will follow both groups looking for signs of heart disease, and if they are correct, subjects who exercise will get less heart disease. With this study design there may be a problem with controlling how much the subjects exercise. In the laboratory, a scientist can control exactly how much an experimental animal exercises, but in the real world this

² The Scandinavian Simvastatin Survival Study Group, *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction*. (1993) 71 Am J Cardiol 393.

³ Doll & Hill, *The mortality of doctors in relation to their smoking habits*. (1954) 328 (7455) BMJ. 1529 .

may be difficult to control. The intervention group may become lazy and not exercise, while the control group might have concern about heart disease and increase exercise, which would affect the study results.

The researchers might attempt a cohort study and follow a large group of people without heart disease over a period of time and ask them detailed questions about exercise and then after several years compare the rate of heart disease among those who exercise regularly to those who do not. Again, if the researchers are correct, patients who exercise regularly will develop less heart disease. One potential problem with this design is that people who exercise regularly may differ in other ways from people who do not exercise regularly. For example, the people who exercise regularly might be more likely to eat healthier and less likely to smoke and have a reduced risk of heart disease that is unrelated to exercise.

The researchers might also choose to perform a case-control study and identify a group of people with heart disease from the hospital coronary care unit as well as a comparable group from the hospital without heart disease. The investigators would then question both groups about their exercise over the past several years and classify each as either exercising regularly or not exercising regularly. Once again, if the researchers are correct, the patients with heart disease will report less exercise than controls. One potential problem with this approach is that people may not be able to remember their exercise patterns, or those with heart disease might feel self-conscious about reporting true exercise patterns and the information obtained about the exposure may not be reliable.

IV. EVALUATING THE ACCURACY OF EPIDEMIOLOGIC STUDIES

A. Accuracy Of An Epidemiologic Study

In an ideal setting, all epidemiologic studies would be designed, conducted, analyzed, and interpreted in a fashion that eliminated sources of error. One of the major goals for epidemiologists is to minimize error as much as possible. Similarly, it is important for those who read and use the epidemiologic literature to be cautious in how the information is interpreted. As such, it is important to understand the factors that can influence the accuracy of epidemiologic study as errors can arise from three main sources – bias, confounding and random error.

Accuracy requires both validity and precision. Bias and confounding affect the validity of a study, while random error affects the precision of a study.

B. Validity

Validity of epidemiologic studies is defined as the “degree to which inferences are warranted given the methods and study population chosen.”⁴ There are two major types of validity – internal validity and external validity. Internal validity represents how well the study findings, aside from random error, represent the truth in the population being studied. The internal validity of an epidemiologic study can be challenged by systematic error caused by either or both of bias and confounding. This systematic error in the study design, conduct, analysis or interpretation can lead to either artificial elevation or artificial

⁴ Oleckno, *Epidemiology: Concepts & Methods* (2008).

reduction in the measures of association between exposure and outcome. External validity, sometimes referred to as generalizability, is the extent to which the results of the study can be applied to populations other than the population under investigation. It is often felt that internal validity is more important than external validity because if a study is not valid, then why would one generalize a non-internally-valid study to another population. The above-mentioned Scandinavian Simvastatin Survival Study⁵ results were believed to be internally valid, and it was also felt to be reasonable to apply these results to other populations.⁶

C. Bias

Bias is a type of systematic non-random error in the design and/or conduct of an epidemiologic study. Bias can have a dramatic effect on the internal validity of a study and because of this, can affect the accuracy of the study. In general, bias can be broken down into two main categories, known as selection bias and information bias. Both of these types of bias can lead to either an overestimation or underestimation of risk in epidemiologic studies. Although bias can be present in all types of studies, bias can be a particularly significant concern in observational studies, especially in those studies that are poorly designed.

Selection bias refers to a systematic error due to the way in which subjects are selected for the study. This type of bias can occur when the subjects in the study population differ from the subjects in the source population. This can occur in a cross-sectional or case-control study when the frequency of the exposure or outcome differs systematically between the study population and the source population. Because of this, selection bias can sometimes lead to an association when one does not actually exist. For instance, an investigator interested in researching whether coffee drinking is associated with a specific type of cancer designs a case-control study and obtains cases from an oncology clinic. The investigator obtains controls from a nearby heartburn clinic. The study is performed, and the investigator finds that coffee drinkers are 1.5 times more likely to develop a specific type of cancer. Since controls are recruited from a different clinic than the cases, it is possible that controls may be systematically different from cases in a way that may affect the study results. In fact, since controls were recruited from a nearby heartburn clinic where patients are routinely instructed to reduce or stop coffee drinking, controls are less likely to be coffee drinkers than all people who would be eligible controls and lead to an overestimate of risk due to selection bias.

Information bias refers to a systematic error due to measurement errors that leads to misclassification of study subjects with regards to either exposure or outcome. Information bias tends to occur during the data collection portion of an epidemiologic study. This misclassification of either exposure or outcome can be characterized as either differential or nondifferential. Differential misclassification can occur when the likelihood of misclassification is different between the study and comparison groups. Differential misclassification may lead to either overestimation or underestimation of the true value of the measure of association. If the cases in a case-control study are more likely to be

⁵ The Scandinavian Simvastatin Survival Study Group. *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction.* (1993) 71 Am J Cardiol 393.

⁶ *Id.*

misclassified as exposed than the controls, then the study will tend to overestimate the true estimate of risk (odds ratio).

For example, suppose an investigator is interested in studying whether high blood pressure is associated with drinking sugary drinks. A case-control study is designed, and the investigator finds 200 cases with high blood pressure and 200 controls with normal blood pressure. The investigator then asks questions about sugary drink habits during the previous five years. The responses are collected and analyzed (table a), and there is a statistically significant increase in risk of high blood pressure with drinking sugary drinks (OR: 3.67; $p < 0.001$), suggesting sugary drinks are associated with high blood pressure. If cases are systematically more likely to report sugary drink usage than controls (differential misclassification because of the belief that sugary drinks may cause high blood pressure), then this will lead to an overestimation of the true estimate of risk. In reality, if there was no increase (table b) in reporting sugary drink consumption among cases (no misclassification), there would be a non-statistically significant estimate of risk (OR: 1.35; $p = 0.13$).

a.

	Study			
	High BP	No high BP		
Sugary drinks	150	90	OR=3.67	P<0.001
No sugary drinks	50	110		
	200	200		

b.

	Truth			
	High BP	No high BP		
Sugary drinks	105	90	OR=1.35	P=0.13
No sugary drinks	95	110		
	200	200		

Nondifferential misclassification can occur when there is likely an equal proportion of misclassification of exposure status among those with and without an outcome or of outcome status among those with and without an exposure. This type of misclassification typically results in a dilution of the effect of exposure on outcome and is more likely to result in no association when an association between exposure and outcome actually exists.

One specific type of bias that leads to misclassification and that is common in case-control studies is known as recall bias. It often results from the fact that cases tend to remember past exposures more than controls. It may also arise if cases are more likely than controls to investigate whether certain risk factors increase the risk of developing a certain disease. Recall bias is often less likely to occur when both cases and controls are patients, for example, in hospitalized patients,⁷ where the degree of thinking about a possible exposure or outcome is likely to be at similar levels. Consider again the above example of the investigator who is trying to determine if there is a relationship between sugary drinks and high blood pressure. If the cases tend to recall and report more sugary drink consumption simply because they have reflected more on their past experiences, recall bias

⁷ Schultz & Grimes, *Case-control studies: research in reverse*. (2002) 359(9304) Lancet 431; Schlesselman, *Case-control studies: design, conduct, analysis* (1982).

could result in an overestimation of the measure of risk between the sugary drinks and high blood pressure.

As particularly pertinent here, in one case-control study involving the potential association between perineal talc use and ovarian cancer,⁸ the investigators examined whether cases and controls reported talc use more frequently if they were interviewed after 2014, which is the year when two widely publicized lawsuits concerning talc use were filed, as opposed to before that year. For those interviewed prior to 2014, approximately the same percentage of cases and controls reported genital talc use (36.5% for cases, 34.0% for controls). For those interviewed after 2014, cases reported talc use 51.5% of the time, while the percentage of controls reporting talc use remained about the same (34.4%). This is a clear demonstration of the effect of recall bias in case-control studies. Critically, that study found a statistically significant risk of ovarian cancer for those who were interviewed after 2014 at 2.91 (95% CI: 1.70-4.97). For those interviewed prior to 2014, no statistically significant association was found.⁹ As discussed in Section VIII.B below, such concerns of recall bias could have affected pre-2014 studies as well.

Selection and information bias can best be controlled and prevented during the design and conduct of a study. This means that investigators must recognize the potential sources of bias and take precautions to minimize this bias. Methods have been developed to prevent or minimize bias in epidemiologic studies. Some of these include attempts to standardize data collection, pilot test data collection instruments, use objective methods to measure exposure and outcome status, verify subject response from other sources and obtain multiple measurements of exposure and outcome status.

D. Confounding

In epidemiology, confounding is a misrepresentation of the true effect of an exposure on an outcome due to an association between the exposure and another factor. This factor is often referred to as a confounder, and like bias, confounding is a systematic, non-random error that can affect the internal validity of a study. Confounding can result in an overestimation or underestimation of the true effect of an exposure on an outcome. In general, for another factor to confound the effect of an exposure on the outcome, three conditions must be met: (1) the factor must be associated with the exposure; (2) the factor must be associated with the outcome; and (3) the factor must not represent a step in the causal pathway between exposure and outcome. Many times, epidemiologists do not know what extra factors will confound an actual effect of an exposure on an outcome, but it is important for suspected factors to be considered as potential confounders. Experienced epidemiologists are usually able to anticipate suspected confounders given previous experience in similar studies or based on previous studies looking at a similar exposure outcome relationship.

The Sister Study, which I discuss in more detail below, is one example of potential confounding affecting the measurement of the effect of genital talc exposure.¹⁰ In that

⁸ Schildkraut et al., *Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)*. (2016) 25(10) Cancer Epidemiol Biomarkers Prev. 1411.

⁹ *Id.*

¹⁰ Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*. (2016) 27 Epidemiology 797.

study, in addition to talc use, participants were also asked about their douching habits. Of the 50,884 women who completed questionnaires, 154 women developed ovarian cancer. Ever douching during the 12 months prior to the study was associated with a statistically significant risk of ovarian cancer (HR: 1.8; 95% CI: 1.2-2.8) when compared with never douching after adjusting for confounders.¹¹ In contrast, there was no statistically significant increase risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use during the 12 months prior to the study when compared with never talc use after adjusting for confounders.¹² There was no change in the estimated effect of talc use after adjustment for douching, and similarly, there was no change in the estimated effect of douching after adjusting for talc use. If those who use talc are more likely to douche, as is demonstrated in this and other studies,¹³ and douching has a significant effect on the risk of ovarian cancer in this study, prior studies that have revealed a significant effect of talc on ovarian cancer may have been confounded by douching.

Although the amount of confounding is the degree to which the measure of association is affected, it is not appropriate to evaluate confounding using statistical tests of significance. In order to ensure the validity of an epidemiologic study, all attempts should be made to control confounding. While bias usually occurs in the study design and data collection phases of an epidemiologic study, confounding usually occurs during the design and analysis phases. Epidemiologists can work to control confounding in the design phase by restricting subjects to only certain characteristics, matching to attempt to create study and comparison groups that are similar with respect to potential confounders, and randomization to decrease confounding by increasing the likelihood that the study group is similar to the comparison group with regard to known factors, as well as unknown potential confounders.

E. Precision

Precision is a measure of the amount of nonsystematic or random error that is present in the study. Random error is variability in a measure that is simply due to chance, and it represents unexplained error in a study. In epidemiologic studies, a precise result would be very easily replicated. Random errors tend to cause inconsistency between different studies and may make it less likely that investigators will find an association between exposure and outcome.

F. Random Error

Random error affects the precision (and thus, the accuracy) of an epidemiologic study. Measurement error and sampling variation are the two main components of random error. Measurement error occurs because of an error in the measuring of the value of a variable. This may be the result of inaccurate measuring devices or due to the subjective type of some exposures or outcomes. Measurement error can be minimized by taking multiple measurements for a certain exposure or outcome. For instance, assume the above case-control study designed to investigate the effect of sugary drinks on blood pressure.

¹¹ *Id.*

¹² *Id.*

¹³ Rosenblatt et al., *Characteristics of women who use perineal powders*. (1998) 92(5) *Obstet Gynecol* 753.

Investigators might consider taking several measures of blood pressure and using the average to minimize measurement error. A second form of random error, sampling variation, can occur because samples used in an epidemiologic study are only estimates of the desired population of interest to study. Consider again the above case-control study in which investigators report the odds ratio of 1.35 as the risk estimate of the effect of sugary drinks on high blood pressure. Suppose the investigators replicated the study using a new sample of the same size and found that the odds ratio was now 1.8. Assuming systematic errors were controlled for in study design, data collection and analysis, this difference can be explained by random error/sampling variation. A third sample might reveal an odds ratio of 1.1 or 2.5, which demonstrates that sampling variation is both unpredictable and not reproducible. In general, epidemiologists try to reduce sampling variation by increasing sample size. The stronger the relationship between the exposure and outcome, the smaller the group of patients that need to be studied for this relationship to be apparent. If the group being studied is too small, then the causal relationship may be missed, or spurious results may show up by sampling variation and random error.

V. STUDY DESIGN CONSIDERATIONS

The purpose of epidemiology is to establish associations between exposures and outcomes that may uncover clues to causation. Epidemiologists can explore the relationship between exposure and outcome in humans in real-world situations by observing (observational study designs) or intervening to a limited extent (experimental study designs), as opposed to controlling all aspects of an experiment in the laboratory. Epidemiologists may also gather data from many studies, either observational or experimental (meta-analysis study designs) and summarize the information in an attempt to demonstrate associations between exposure and outcome. As such, there are many different study designs in epidemiologic research in humans, each with strengths and weaknesses.

A. Case Reports And Case Series

Individual level observations can be documented in a case report, a particular clinical situation involving one unique patient, or in a case series, a description of a group of patients with similar clinical findings or conditions. Case reports and case series are helpful tools in generating hypotheses about associations between exposures and outcomes. However, the lack of a comparison group and the likely presence of bias and confounding limit validity, and therefore limit the ability of these types of epidemiologic descriptions to establish causal associations between exposure and outcome.

B. Cross-Sectional Studies

A common epidemiologic study design used in the initial attempts to evaluate associations between exposures and outcomes is the cross-sectional study. In this type of study, both the exposure and outcome are evaluated simultaneously in each study participant. This approach is sometimes referred to as a prevalence study, as cases of disease or outcome identified are prevalent cases of the outcome being investigated. It is impossible to determine the temporality between exposure and outcome with this epidemiologic study design because of the temporal bias that may exist if the disease causes the exposure. For instance, prevalent cases of asthma may be less likely to own a cat than those without asthma. As patients with asthma may have been instructed to not own a cat,

this relationship might lead investigators to conclude that cat ownership is protective against asthma, leading to a phenomenon known as reverse causality. In addition to temporal bias, selection bias due to survivorship may also be present in cross-sectional studies. This may result if exposure in cases leads to shortened survival than those cases who are unexposed. Similar to case-reports and case-series, cross-sectional studies are often used to generate hypotheses about potential causal associations between exposure and outcome.

C. Case-Control Studies

Another common study design used to evaluate the effect of an exposure on an outcome is known as a case-control study. In this type of epidemiologic study, cases are defined as those with a particular outcome and non-cases or controls are defined as those without a certain outcome. Exposure is then retrospectively evaluated and compared between the cases and controls. Thus, in a case-control study, the prevalence of the exposure of interest should be higher among those with the outcome (cases) than those without the outcome (controls). In general, case-control studies provide more information on the temporal relationship between exposure and outcome than cross-sectional studies. However, case-control studies remain susceptible to other forms of bias. Selection bias can occur in a case-control study when the relationship between exposure and outcome differs systematically between the study population and the source population. Because of this, selection bias can sometimes lead to an association when one does not actually exist. Recall bias is common in case-control studies and results from the cases or subjects with disease having a tendency to remember past exposures more than controls. As mentioned above, it may also arise if cases are more likely to investigate possible factors that may increase the risk of developing a certain disease. Recall bias is often less likely to occur when both cases and controls are patients, for example, in hospitalized patients¹⁴ as compared to population-based case-control studies where the degree of thinking about a possible exposure or outcome is likely to be at similar levels.

D. Cohort Studies

A cohort design assigns an individual as either exposed or unexposed and then that individual is followed over time to see if a particular outcome of interest develops. In general, there are two main types of cohort studies – prospective and retrospective. A prospective cohort design establishes exposure status in the beginning of a study and potentially repeatedly during the study, and then the outcome status for each individual is determined during a follow-up period that extends into the future. In a retrospective cohort design, the exposure and outcome have already occurred (as in the use of administrative or registry data), and the exposure status of each individual is determined from a time period that existed in the past with the outcome then being determined during a time period after exposure that may extend to the present. Temporality is established whether a cohort study is prospective or retrospective in design because the exposure status is always determined prior to evaluating outcome status. In general, cohort studies provide more evidence for a causal relationship between exposure and outcome, and can often study many exposure-outcome relationships with less chance for bias and confounding than case-control studies if

¹⁴ Oleckno (2008) at 207; Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Severe Childhood Diseases?* (2003) 157(2) *Am J Epidemiol* 176.

the design, conduct, data collection and analysis are properly performed. However, cohort study designs also remain susceptible to certain types of bias and confounding, are often very expensive, take a long time to conduct and may be difficult to perform, especially if the outcome of interest is rare.

E. Experimental Studies

Unlike an observational study, where exposure is not under the control of the investigator, an experimental study is one in which the exposure (intervention) is controlled directly by the investigator. One such experimental study design – the randomized-controlled clinical trial – is a planned epidemiologic experiment where subjects are randomly assigned to an exposure (intervention) or control group to evaluate the effect of the exposure on outcome. Randomized controlled clinical trials are considered the gold standard of epidemiologic studies. Although there are many advantages to an experimental study design, experimental studies are still subject to the effects of bias and confounding if not designed and conducted properly, and there are instances when this design is not suitable to evaluate the causal association between exposure and outcome because of potential for harm, lack of equipoise or ethical concerns.

F. Meta-Analysis

Epidemiologists may use multiple studies that address the same research question to provide an overall statistical summary of the results. This process is known as meta-analysis and is useful when individual studies tend to be inconclusive because of small sample size. A meta-analysis can provide a precise estimate of the effect of an exposure on an outcome of interest by combining the results of relevant studies by using a systematic approach and analysis. Meta-analyses can also help to provide consensus about the effectiveness of interventions, as well as insight or explanation for differences in individual trial results. Meta-analysis is a type of systematic review that utilizes a comprehensive, rigorous and standardized approach to selecting, assessing and synthesizing all relevant studies on a given topic. Systematic reviews that summarize studies without combining the results statistically are often called qualitative systematic reviews, while those that also combine study results statistically to produce an overall summary effect are referred to as quantitative systematic reviews, and are synonymous with meta-analyses. There are fundamental steps that must be followed to ensure the quality of a meta-analysis. These include (a) defining the research question, (b) defining the criteria for study selection, (c) structuring a review of the literature for all eligible studies, (d) structuring data abstraction, (e) reviewing the methods and results of each study critically, (f) summarizing the results of each study using a standard format, (g) using proper statistical tests to provide a summary effect, (h) assessing variation (heterogeneity) between studies and (i) reviewing, interpreting and reporting the findings.¹⁵

The idea of a meta-analysis is to combine the results of individual studies so that a summary point estimate can be reached that describes the strength of association between exposure and outcome. There are different approaches to modelling data between studies, and it is important to understand that these approaches may produce different results. Fixed-effects models assume that the effect of exposure on outcome is equal in all studies

¹⁵ Oleckno (2008).

included in the meta-analysis, while random-effects models assume that the effect of exposure on outcome varies between each included study due to both actual differences in effect and random error. In general, when the findings of the included studies are similar, both models yield similar summary estimates, but when the findings of the included studies vary appreciably, the models may produce conflicting results. A statistical test of heterogeneity is oftentimes performed to evaluate whether differing results from the included studies are due to chance alone. If unlikely due to chance, then a random effects model may be more appropriate.

It is also important to understand that in addition to the great deal of preparation and structured organization that is involved in conducting a meta-analysis, it is of utmost importance to vigilantly examine the accuracy of the included individual studies when relying on meta-analyses. Many of plaintiffs' epidemiologists, for instance, premise their causation opinions in large part on the various meta-analyses assessing the effect of exposure to talc on ovarian cancer.¹⁶ But, when it comes to concerns over bias and confounding, a pooled analysis or a meta-analysis will only be as good as the included studies. And while some of plaintiffs' experts have performed their own meta-analyses, the underlying limitations of the included studies are not lessened or removed simply by performing additional meta-analyses using the same studies with different groupings.

VI. EPIDEMIOLOGIC STUDIES OF TALC POWDER AND OVARIAN CANCER

In order to understand the relationship between talc exposure and ovarian cancer, I have performed a search of the peer-reviewed literature. I identified 44 individual studies investigating the exposure/outcome relationship between talcum powder use and ovarian cancer. The individual studies were evaluated with attention to study design, accuracy, exposure assessment, analysis and validity, while noting both strengths and weaknesses.

A. Summary Of Article Study Designs

Due to the exposure (talc powder) and outcome (ovarian cancer) being studied, there were no experimental studies, as this study design would not be suitable to evaluate this relationship. The studies identified can be separated into three categories: (1) case-control studies, (2) cohort studies, and (3) meta-analyses. I reviewed 33 case-control studies (two of which pooled data from different studies), four cohort studies, and seven meta-analyses published between 1982 and 2018.¹⁷

The 33 case-control studies ranged in size from 123 to 4,092 participants. There were seven hospital-based case-control studies and 26 population-based case-control studies that I reviewed. The assessment of exposure varied extensively in the case-control studies and was obtained from responses to questionnaires on the use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, not genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on

¹⁶ Clarke-Pearson Rep. 7; McTiernan Report 8, 63; Moorman Rep. 10.

¹⁷ I also briefly reviewed the unpublished Taher meta-analysis cited by several of plaintiffs' experts, and it does not affect my analysis. The association it reports is not materially higher than prior studies, and it agrees with IARC's assessment that a causal relationship is merely "possible" in light of current evidence.

diaphragms, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/ perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. All studies included pathologically confirmed cases or cancer registry cases of ovarian cancer. Analyses varied widely among the case-control studies from no adjustment for potential confounders to adjusting for varying degrees of confounding, including age at first birth, age at last birth, age at menarche, age at menopause, tumor behavior, breast feeding, community-based case-control study, diaphragm use, duration of use, exercise, education, frequency of use, family history of breast and ovarian cancer, histologic type, hospital-based case-control study, hair dye use, hormone replacement therapy, hysterectomy, income, use of medications, menopausal status, sanitary napkin use, number of pregnancies, oral contraceptive use, parity, socioeconomic status, timing of use and tubal ligation.

The four cohort studies I reviewed utilized data from the US Nurses' Health Study (NHS), US Nurses' Health Study II, the Women's Health Initiative Observational Study, and the Sister Study and ranged in size from 41,654 to 108,870 participants. The assessment of exposure was obtained from responses to questionnaires on talc use, talc on the perineum or napkin, powder on the genitals, powder on diaphragm, powder on napkin or talc use in the past 12 months. Analyses varied across the different cohort studies with varying degrees of adjustment for potential confounding, including age, age at last birth, menopause status, age at menopause, race, parity, BMI, activity level, breast feeding, oral contraceptive use, duration of oral contraceptive use, estrogen use, postmenopausal hormone use, duration of hormone replacement therapy, tubal ligation, smoking status and family history of breast or ovarian cancer.

B. Case-Control Studies: Hospital-Based

I identified seven hospital-based case-control studies that have evaluated the potential causative association between talc and ovarian cancer, yielding similar non-statistically significant estimates of risk of ovarian cancer and talc usage.

In 1983, Hartge et al.¹⁸ conducted a hospital-based case-control study of pathologically identified ovarian cancer and frequency matched controls of women in the same hospitals in Washington, DC. Interviews were performed and exposures were categorized as "any" use of talc and "genital" exposure to talc. Among women exposed to "any" talc, the odds ratio of ovarian cancer was not statistically significant at 0.7 (95% CI: 0.4-1.1). Among those who reported talc use on genitals, sanitary napkin or underwear, the odds ratio was not statistically significant at 2.5 (95% CI: 0.7-10.0). The study is limited by small sample size and lack of adjustment for potential confounders.

In 1988, Whittemore et al.¹⁹ similarly completed a hospital-based case-control study of histologically confirmed ovarian cancer cases in pre-menopausal and postmenopausal women between the ages of 18 and 74 with primary epithelial ovarian cancer in Santa Clara County hospitals or at the University of California, San Francisco Medical Center and

¹⁸ Hartge et al., *Talc and Ovarian Cancer*, (1983) 250 J. Am. Med. Ass'n 1844.

¹⁹ Whittemore et. al., *Personal And Environmental Characteristics Related To Epithelial Ovarian Cancer*, (1988) 128 Am J. Epidemiol 1228.

hospitalized controls. In-person interviews were performed, and to evaluate exposure, subjects were asked about whether they had used talcum powder products on the perineum, sanitary pads and/or diaphragms. Participants who responded were asked about frequency and duration of use. Among women who reported perineum only talc use, the odds ratio was not statistically significant at 1.45 (95% CI: 0.81-2.60) after adjustment for parity and oral contraceptive use. There was no trend in increasing duration of treatment, and the risk of ovarian cancer was not statistically significant with increasing frequency of use.

Booth et al.²⁰ in 1989 performed a hospital-based case-control study of pathologically identified ovarian cancer in women under 65 years of age from 13 hospitals in London and two in Oxford and hospitalized controls. Subjects were interviewed and exposure was obtained through a questionnaire and frequency of talc use was reported as never, rarely, monthly, weekly or daily talc use. There was no statistically significant increase in risk of ovarian cancer between never and daily reported talc use (OR: 1.3; 95% CI: 0.8-1.9) after adjusting for age and social class. There was no trend of increased risk of ovarian cancer with increased frequency of reported talc use, as those participants who reported weekly use had a higher risk estimate (OR: 2.0; 95% CI: 1.3-3.4) than those who reported daily talc use, and no dose-response relationship with frequency of reported talc use was found among those exposed compared to those unexposed after adjusting for age and social class.

Rosenblatt et al.²¹ in 1992 reported a hospital-based case-control study evaluating “fiber exposure” generally (with “fiber” defined as asbestos, talc or fiberglass), including “genital fiber use” specifically, which included an assessment of “method of application” in pathologically confirmed cases of ovarian cancer and hospitalized controls between 1981 and 1985 at the Johns Hopkins Hospital. A questionnaire was administered to participants, both by telephone and in the hospital, which was used to obtain reported exposure to talc and presence and length of applying talcum powder to the genital area. There was no statistically significant increase in risk of ovarian cancer with “genital fiber use” (OR: 1.0; 95% CI: 0.2-4.0) after adjustment for parity, or for exposures from diaphragm use with powder (OR: 3.0; 95% CI: 0.8-10.8) after adjustment for parity and education, or genital bath talc exposure (OR: 1.7; 95% CI: 0.7-3.9) in unadjusted analysis. There was also no statistically significant increase in the risk of ovarian cancer with length of exposure (≥ 37.4 years vs. < 37.4 years) to “genital fiber use” (OR: 2.4; 95% CI: 1.0-5.8) after adjustment for religion.

Tzonou et al.²² in 1993 conducted a case-control study among hospitalized patients from two hospitals in Athens, Greece with histologically confirmed ovarian cancer and hospital visitor controls. In-hospital questionnaires were administered and exposure was obtained as reported use of talc in the perineal region. Even though the prevalence of talc usage was low, there was no statistically significant association between reported exposure of talc to the perineum and risk of ovarian cancer (OR: 1.05; 95% CI: 0.28-3.98). The

²⁰ Booth et al., Risk factors for ovarian cancer: a case-control study. (1989) 60(4) *Br J Cancer*. 592.

²¹ Rosenblatt et al., *Mineral Fiber Exposure and the Development of Ovarian Cancer*, (1992) 45 *Gynecologic Oncology* 20.

²² Tzonou et al., *Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer*. (1993) 55(3) *Int J Cancer*. 408.

authors adjusted for age, years of schooling, weight before onset of the disease, age at menarche, menopausal status, age at menopause, parity, age at first birth, tobacco smoking, consumption of alcoholic beverages, consumption of coffee, hair dyeing and analgesics-tranquilizers/hypnotics.

Hartge and Stewart²³ in 1994 reported a case-control study of women diagnosed with pathologically confirmed ovarian cancer in the Washington, DC area between 1978 and 1981. This study analyzed occupational history in women who were diagnosed with ovarian cancer and hospital-based controls. Trained interviewers used a standardized questionnaire that included lifetime job history and exposure to talc on the job. An industrial hygienist conducted an industrial hygiene exposure assessment evaluating each job/industry combination for potential exposure to talc, as well as other potential exposures. The risk of ovarian cancer was not significantly increased for any exposure to talc, regardless of the duration of exposure: <5 years (OR: 0.5; 95% CI: 0.1-1.4), 5-9 years (OR: 0.3; 95% CI: 0.1-1.4), 10+ years (OR: 0.5; 95% CI: 0.2-1.5).

Wong et al.²⁴ in 1999 reported the results of a hospital-based case-control study in patients with ovarian cancer as determined by the Roswell Park Tumor Registry and hospital-based controls. Exposure was evaluated using a self-administered questionnaire regarding medical history and personal hygiene. There was no statistically significant increased risk of ovarian cancer among participants who ever used talc (OR: 1.13; 95% CI: 0.88-1.44)²⁵ or among those who used talc on both a sanitary napkin and on the genital or thigh area (OR: 1.1; 95% CI: 0.7-1.7). There was a haphazard non-statistically-significant relationship with duration of talc use over time and risk of ovarian cancer: 1-9 years (OR: 0.9; 95% CI: 0.6-1.5), 10-19 years (OR: 1.4; 95% CI: 0.9-2.2), and ≥20 years (OR: 0.9; 95% CI: 0.6-1.2) after adjustment for parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location and history of tubal ligation or hysterectomy.

C. Case-Control Studies: Population-Based

I identified 26 population-based case-control studies (two from pooled data) that assessed the potential causative association between talc and ovarian cancer, yielding conflicting results.

Cramer et al.²⁶ in 1982 reported the first epidemiologic case-control study of genital talc use and risk of ovarian cancer. Cases were women diagnosed with ovarian cancer in the Greater Boston area between 1978 and 1981 and identified through pathology logs or tumor boards and confirmed pathologically. Controls were identified through annual

²³ Hartge & Stewart., *Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981*. (1994) 36(8) J Occup Med. 924.

²⁴ Wong et al. *Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study*. (1999) 93 Obstet Gynecol 372.

²⁵ The Wong paper does not report an odds ratio for ever versus never talc use, but the text of the article contains the information necessary to calculate it. Specifically, the text reports that 221 cases out of 421 total had ever used talc and 311 controls out of 693 total had ever used talc. The calculated odds ratio is 1.13 with a 95% CI of 0.88-1.44 (STATA SE 15.1, StataCorp, College Station, TX).

²⁶ Cramer et al., *Ovarian cancer and talc: a case-control study*. (1982) 50(2) Cancer 372.

listings of Massachusetts residents and were matched by residence, race and age. Subjects were interviewed in person to evaluate potential exposure to talc through contraceptives, hygiene or surgery. After adjustment for parity and menopausal status, a statistically significant association was found between “any perineal exposure” of talc and risk of ovarian cancer (OR: 1.92; 95% CI: 1.27-2.89).

Harlow and Weiss²⁷ in 1989 conducted a study of perineal use of powder and the risk of borderline ovarian cancer. Caucasian women aged 20-79 from three counties in Washington State diagnosed as having serous or mucinous borderline ovarian tumor were identified using the Seattle-Puget Sound Cancer Surveillance System during the years 1980 to 1985. Independent pathologic review was performed on 73% of cases. A control group was identified through random digit dialing. Reproductive, sexual and medical history, as well as information on talc exposure, was obtained during an in-person interview. There was no statistically significant increase in risk of borderline ovarian tumors with any perineal exposure to powder (OR: 1.1; 95% CI: 0.7-2.1), baby powder use (OR: 0.8; 95% CI: 0.4-1.9), or unspecified talc use (OR: 1.0; 95% CI: 0.4-2.4) after adjusting for age, parity and use of oral contraceptives. Use of deodorizing powder alone (OR: 3.5; 95% CI: 1.2-28.7) and use of deodorant powder alone or in combined use with another powder (OR: 2.8; 95% CI: 1.1-11.7) were both associated with a statistically significant increase in risk of borderline ovarian tumors after adjusting for age, parity and use of oral contraceptives.

Harlow et al.²⁸ in 1992 reported a case-control study among women 18 to 76 years of age diagnosed with borderline or malignant epithelial ovarian cancer confirmed pathologically from 10 hospitals in the Boston metropolitan area. Controls were selected from the Massachusetts Town Books. An in-person interview was performed to obtain demographic, occupational and medical history, as well as hygienic practices. Exposure was reported as any genital talc, type of application (sanitary napkin, underwear, partner or application to diaphragm, or dusting powder to the perineum) and brand of application (brand or generic baby powder or deodorizing or other scented powders). Application via dusting to the perineum was associated with a statistically significant risk of ovarian cancer (OR: 1.7; 95% CI: 1.1-2.7) after adjusting for parity, education, marital status, religion, use of sanitary napkins, douching, age and weight. Use of any genital talc was not associated with a statically significant increase in risk of ovarian cancer (OR: 1.5; 95% CI: 1.0-2.1) after adjusting for the same potential confounders. Although there was no statistically significant increase in risk of ovarian cancer with increasing lifetime total applications of talc-containing powders after adjusting for the same potential confounders, there was a statistically significant increase in the risk of ovarian cancer with more than 10,000 total lifetime perineal applications of talc-containing powders in participants with hysterectomy, tubal ligation and use during nonovulatory months (OR: 2.8; 95% CI: 1.4-5.4).

Chen et al.²⁹ in 1992 conducted a case-control study in China in women with pathologically confirmed cases of epithelial ovarian cancer. Controls were identified from

²⁷ Harlow & Weiss, *A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc*. (1989) 130(2) Am J Epidemiol. 390.

²⁸ Harlow et al., *Perineal exposure to talc and ovarian cancer risk*. (1992) 80(1) Obstet Gynecol. 19.

²⁹ Chen et al., *Risk factors for epithelial ovarian cancer in Beijing, China*. (1992) 21(1) Int J Epidemiol. 23.

the community using a random selection from a neighborhood committee or village. A questionnaire was developed and administered through face-to-face interviews by trained interviewers. There was no statistically significant association with using dusting powder to the lower abdomen and perineum and risk of ovarian cancer (OR: 3.9; 95% CI: 0.9-10.6) after adjusting for education and parity.

Cramer and Xu³⁰ in 1995 reported on a case-control study of women in the Greater Boston area diagnosed with ovarian cancer. The study combined women diagnosed with ovarian cancer from area hospitals between 1984 and 1987 and confirmed pathologically with a previous study of women diagnosed between 1978 and 1981. Controls were selected from the general population and matched by age and residence. In an unadjusted analysis, talc use was associated with an increase in risk of ovarian cancer (OR: 1.6; 95% CI: 1.2-2.1).

In 1995, Purdie et al.³¹ conducted a case-control study in three Australian states of women diagnosed with ovarian cancer that was confirmed pathologically. Controls were drawn at random from the electoral roll and stratified by age and geographic region. Trained interviewers administered a questionnaire in a face-to-face interview, which included questions about marital status, education, ethnicity, height, weight, smoking history, occupation, medical history and history of talc use. Talc use around the abdomen/perineum was associated with an increased risk of ovarian cancer (OR 1.27; 95% CI: 1.04-1.54) after adjusting for parity.

Green et al.³² in 1997 performed a case-control study using the study population from the Purdie study. Methods for case and control identification were similar to the Purdie study. Ever douching was associated with a non-significant 60% increase in risk of ovarian cancer. Use of talc in the perineal region was associated with an increased risk of ovarian cancer (OR: 1.3; 95% CI: 1.1-1.6) after adjustment for parity, oral contraceptive use, age, education, body mass index, smoking and family history of ovarian cancer. Even though there was a reported 60% increase in risk of ovarian cancer for those who ever-douched, there were no adjustments in multivariable analyses for douching as a potential confounder.

Shushan et al.³³ in 1996 conducted a case-control study of women aged 36 to 64 years with histologically diagnosed primary invasive or borderline epithelial ovarian cancer. Cases were identified through the Israel Cancer Registry. Controls were identified by telephoning randomly selected numbers within the same area codes as the cases. Cases and controls were interviewed using a questionnaire containing details on medical history and exposures. Exposure to talc was recorded as never-seldom and moderate-a lot talc use. A

³⁰ Cramer & Xu, *Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer*. (1995) 5 Ann Epidemiol. 310.

³¹ Purdie et al., *Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study*. Survey of Women's Health Study Group. (1995) 62(6) Int J Cancer. 678.

³² Green et al., *Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer*. Survey of Women's Health Study Group. (1997) 71(6) Int J Cancer. 948.

³³ Shushan et al., *Human menopausal gonadotropin and the risk of epithelial ovarian cancer**. (1996) 65(1) Fertil Steril. 13.

larger proportion of cases reported moderate-a lot of talc use when compared with controls (10.5% vs. 5.6%; $p=0.04$) without adjusting for potential confounders.

Chang and Risch³⁴ in 1997 reported a case-control study among women diagnosed with histologically confirmed borderline and invasive ovarian cancers in Toronto and southern Ontario. Controls were identified through the Ontario Ministry of Finance and random selection based on geographic residence. A questionnaire was developed and administered in-person, in-home. Exposure to talc was evaluated by reported regular talc use, use of talc/cornstarch combination, talc use with a sanitary napkin, talc use after bathing as well as after bath uses per month, and years of after bath use. Although there was a significant increase in risk of ovarian cancer with any talc exposure (OR: 1.42; 95% CI: 1.08-1.86), there was no dose-response, and in fact there was a non-statistically significant inverse trend for after bath uses per month: <10 (OR: 1.84; 95% CI: 1.24-2.73), 10-25 (OR: 1.13; 95% CI: 0.74-1.72), >25 (OR: 0.95; 95% CI: 0.61-1.49) and for years of after bath use: <30 (OR: 1.7; 95% CI: 1.09-2.64), 30-40 (OR: 1.44; 95% CI: 0.96-2.15), >40 (OR: 0.87; 95% CI: 0.54-1.38) after adjusting for age at time of interview, years of oral contraceptive use, number of full-term pregnancies, average duration of breastfeeding per pregnancy, the occurrence of a tubal ligation or hysterectomy, and having a mother/sister with ovarian or breast carcinoma.

Cook et al.³⁵ in 1997 conducted a case-control study of women diagnosed with invasive or borderline epithelial ovarian cancer from records of the Cancer Surveillance System of western Washington State from 1986 through 1988. Controls were identified by random digit dialing of a larger control pool for other studies of cancer in women. Information regarding genital powder exposure was collected by in-person interviews. The occurrence of lifetime genital powder application and the exclusive use of types of genital powder application, including perineal dusting, diaphragm storage in powder, powder on sanitary napkins and genital deodorant spray, were collected. Reported exposure also included cumulative lifetime days of use for perineal dusting, cumulative lifetime months for diaphragm storage in powder, cumulative lifetime months for powder on sanitary napkins and cumulative lifetime months for genital deodorant spray. The use of different types of powder, including talcum powder, baby powder, cornstarch, deodorizing powder, bath or body powder and unspecified powder, was also reported. Although there was an increase in risk of ovarian cancer in women who dusted their perineal areas with powder after bathing (OR: 1.8; 95% CI: 1.2-2.9), there was no statically significant increase in risk of ovarian cancer with increasing cumulative lifetime days of any perineal dusting. There was also no statistically significant increase in risk of ovarian cancer with exclusive use of talcum powder (OR: 1.2; 95% CI: 0.6-2.5) or with the use of any talcum powder (OR: 1.6; 95% CI: 0.9-2.8) after adjusting for age.

Godard et al.³⁶ in 1998 reported a case-control study of women with histologic diagnosis of ovarian cancer through the gynecologic oncology clinics of two large teaching

³⁴ Chang & Risch, *Perineal talc exposure and risk of ovarian carcinoma*. (1997) 79(12) Cancer. 2396.

³⁵ Cook et al., *Perineal powder exposure and the risk of ovarian cancer*. (1997) 145(5) Am J Epidemiol. 459.

³⁶ Godard et al., *Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study*. (1998) 179(2) Am J Obstet Gynecol. 403.

hospitals in Montreal in 1995 and 1996. Controls were obtained through random digit dialing. A questionnaire was developed and administered either in-person or on the phone to obtain medical history and reported exposure to talc on perineum. Talc on the perineum was not statistically associated with an increase in ovarian cancer (OR: 2.49; 95% CI: 0.94-6.58) after adjusting for age at diagnosis, age at last childbirth, age at menarche, age at last oral contraceptive use, tubal ligation or hysterectomy and alcohol use.

Cramer et al.³⁷ in 1999 conducted a case-control study of women with newly diagnosed ovarian cancer in eastern Massachusetts or New Hampshire identified through tumor boards and statewide cancer registries with review of pathology reports. Controls were identified through random digit dialing. Participants were interviewed in-person using a standardized questionnaire and asked if they regularly used talc, baby powder, or deodorant powder dusted or sprayed on “feet, arms, or other non-genital areas, to the genital or rectal area, on sanitary napkins, or on underwear” as well as a husband’s use of powder in his genital area. “[T]ypes of powder(s) used, applications per month and total years of use were assessed in talc users.” Any reported personal genital exposure was associated with increased risk of ovarian cancer (1.60; 95% CI: 1.18-2.15) after adjusting for age, study center, tubal ligation, BMI, parity, oral contraceptive use, or primary relative with breast or ovarian cancer. Risk of ovarian cancer increased and then fell (inverse relationship) with increasing years of talc use and with increasing total applications, although these estimates were not statistically significant.

Ness et al.³⁸ in 2000 reported a case-control study of women diagnosed with ovarian cancer who were identified from 39 hospitals in the Delaware Valley region. Controls were identified through random digit dialing. Statistically significant associations were observed for the use of talc on the feet, etc. (OR: 1.4; 95% CI: 1.1-1.6), the genital/rectal area (OR: 1.5; 95% CI: 1.1-2.0), sanitary napkins (OR: 1.6; 95% CI: 1.1-2.3) and underwear (OR: 1.7; 95% CI: 1.2-2.4) after adjusting for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy and breast-feeding. Risk of ovarian cancer increased and then fell (inverse relationship) with increasing years of talc use and with increasing total applications, although these estimates were not statistically significant.

Mills et al.³⁹ in 2004 reported a case-control study of epithelial ovarian cancer in 22 counties of Central California and identified cases through two regional cancer registries as women diagnosed with pathologically confirmed epithelial ovarian cancer from 2000 through 2001. Controls were women 18 years or older selected by random digit dialing. All cases and controls were interviewed by telephone to obtain information on history of adult use of talcum powder in the genital area, calendar year(s) of use, frequency of use, and total duration of use. Although there was a statistically significant increase in risk of ovarian cancer with ever talc use (OR: 1.37; 95% CI: 1.02-1.85) after adjusting for age, race/ethnicity, duration of oral contraceptive use and breast feeding, there was no clear

³⁷ Cramer et al., *Genital talc exposure and risk of ovarian cancer*. (1999) 81(3) Int J Cancer. 351.

³⁸ Ness et al., *Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer*. (2000) 11(2) Epidemiology 111.

³⁹ Mills et al., *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*. (2004) 112 Int’l J. Cancer 458.

dose-response with relation to frequency and duration of talc use and risk of ovarian cancer after adjusting for the same potential confounders. There was a haphazard relationship between reported frequency of use and risk of ovarian cancer, with estimates increasing with rare to several time a month use, then decreasing with 1-3 times per week, and finally increasing with 4-7 times per week. Similarly, there was a haphazard relationship between duration of use and risk of ovarian cancer, as estimates increased at 4-12 years, then decreased at 13-30 years and decreased further at >30 years reported exposure.

Pike et al.⁴⁰ in 2004 conducted a case-control study of women in Los Angeles County with histologically confirmed ovarian cancer or borderline tumors identified by the Cancer Surveillance Program between 18 and 74 years of age from 1992 to 1998. Controls were identified using a systematic algorithm based on the address of the patient. Participants were interviewed in person using a questionnaire covering medical and personal lifestyle history. Genital area talc usage was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.60; 95% CI: 1.18-2.18) after adjustment for ethnicity, age, education, family history of ovarian cancer, tubal ligation, BMI, parity, age at last childbirth, number of births, number of incomplete pregnancies, oral contraceptive use, menopausal status, age at menopause and estrogen-progesterone therapy.

Jordan et al.⁴¹ in 2007 reported a case-control study of women aged 18-79 years with histologically confirmed invasive and borderline ovarian cancer in Australia identified by the Australian Ovarian Cancer Study and state-based cancer registries between 2002 and 2005. Women with benign mucinous tumors were also identified by the Australian Ovarian Cancer Study and through records from three major pathology laboratories. Controls were randomly selected from the Australian Electoral Roll after stratifying for age and state. Participants were asked to complete and return a health and lifestyle questionnaire. Neither moderate talc use in the perineal region (OR: 0.4; 95% CI: 0.1-2.0) nor substantial talc use in the perineal region (OR: 1.0; 95% CI: 0.4-2.1) was associated with a statistically significant increase in risk of invasive mucinous ovarian cancer after adjustment for age, education level, parity, use of oral contraceptives, hysterectomy, tubal ligation and smoking status.

Gates et al.⁴² in 2008 reported a nested case-control study of talc use, variants in the GSTM1, GSTT1 and NAT2 genes, and the risk of ovarian cancer using cases from the New England Case-Control Study (NECC) and the Nurses' Health Study (NHS). The "NECC questionnaires included multiple questions about regular use of talcum, baby or deodorizing powder as an adult. Specific questions were asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear or non-genital areas), frequency of use, age at first use, number of years used and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby

⁴⁰ Pike et al., *Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study*. (2004) 82(1) Fertil Steril. 186.

⁴¹ Jordan SJ, Green AC, Whiteman DC, Webb PM, Australian Ovarian Cancer Study Group. *Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum?* (2007) 107(2) Gynecol Oncol 223.

⁴² Gates et al., *Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer*. (2008) 17(9) Cancer Epidemiol Biomarkers 2436.

or deodorizing powder to the perineal area (no, <once/week, 1-6 times/week or daily) or to sanitary napkins (yes/no).” There was a statistically significant increase in the risk of ovarian cancer with regular genital talc use in participants from the NECC study (OR: 1.62; 95% CI: 1.26-2.09) but no statistically significant increase in risk of ovarian cancer with regular talc use in the NHS (OR: 1.48; 95% CI: 0.82-2.68). Similarly, there was a statistically significant increase in the risk of ovarian cancer with daily genital talc use in participants from the NECC study (OR: 1.61; 95% CI: 1.18-2.2) but no statistically significant increase in risk of ovarian cancer with regular talc use in the NHS (OR: 1.34; 95% CI: 0.65-2.76). Regular genital talc use was associated with a statistically significant increase in risk of ovarian cancer using the combined study population (OR: 1.36; 95% CI: 1.14-1.63) after adjustment for duration of oral contraceptive use, parity, tubal ligation, BMI and duration of hormone replacement therapy. There was no clear dose-response with regard to frequency of genital talc use, with estimates falling with less than once a week usage and then rising with 1-6 times a week and daily usage.

Merritt et al.⁴³ in 2008 reported the Australian Ovarian Cancer Study, which was an Australia-wide case-control study of epithelial ovarian cancer. Cases were women diagnosed with invasive or low malignant potential ovarian cancer aged 18 to 79 years between 2002 and 2005. Controls were selected from the Australia Electoral Roll. Study participants filled out a comprehensive health and lifestyle questionnaire. “To determine use of talcum powder in the perineal region, participants were asked whether they had ever used powder or talc in the genital area or on underwear or sanitary pads/diaphragm. They were asked their age at first use and years of talc use in these areas.” Ever perineal use of talcum powder was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.17; 95% CI: 1.01-1.36) after adjusting for age, education, parity and oral contraceptive use. However, there was no clear dose-response relationship, with a random shape of the exposure-response curve between perineal use of talcum powder and risk of ovarian cancer as well as the risk of cancer subtypes.

Moorman et al.⁴⁴ in 2009 reported a case-control study of epithelial ovarian cancer conducted in a 48-county region of North Carolina between 1999 and 2008. Cases were identified through the North Carolina Cancer Registry and were confirmed histopathologically. Controls were obtained from the same geographic region through random digit dialing. In-person questionnaires were administered, which included questions on medical history and lifestyle factors, including talc ever use. There was no statistically significant increase in risk of ovarian cancer with ever talc use among both white women (OR: 1.04; 95% CI: 0.82-1.33) and African Americans (OR: 1.19; 95% CI: 0.68-2.09) after adjusting for age.

In 2009, Wu et al.⁴⁵ conducted a case-control study of residents of Los Angeles County between the ages of 18 and 74 who had histologically confirmed invasive or

⁴³ Merritt et al., *Talcum Powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer*. (2008) 122 Int’l J. Cancer 170.

⁴⁴ Moorman et al., *Ovarian Cancer Risk Factors in African-American and White Women*. (2009) 170(5) Am J Epidemiol 598.

⁴⁵ Wu et al., *Markers of inflammation and risk of ovarian cancer in Los Angeles County*. (2009) 124 Int’l J. Cancer 1409.

borderline ovarian cancer diagnosed from 1998 through 2002. Cases were identified by the Cancer Surveillance Program. Controls were identified using a neighborhood recruitment algorithm. Participants were interviewed using a questionnaire that covered medical, gynecological, reproductive and lifestyle history. To determine use of talcum powder, subjects were asked if they ever used talc at least once per month for six months or more. If the response was positive, participants were asked if “they had ever used talc in nonperineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm,” as well “frequency of use (times per month) and years of talc use.” Ever talc use was associated with a statistically significant risk of ovarian cancer (OR: 1.48; 95% CI: 1.15-1.91) as was talc applied to the perineal area (OR: 1.53; 95% CI: 1.13-2.09) after adjusting for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity. A statistically significant increase in risk of ovarian cancer was also seen in those who used talc for more than 20 years and more than 30 times per month (OR: 2.08; 95% CI: 1.34-3.23) and in those who had more than 52,000 talc uses (OR: 1.99; 95% CI: 1.34-2.96).

Rosenblatt et al.⁴⁶ in 2011 reported a case-control study of women from a 13-county area of Washington State who were 35 to 74 years old and who were diagnosed with invasive or borderline epithelial ovarian tumor between 2002 and 2005. Cases were identified through the Cancer Surveillance System and controls were selected by random digit dialing. In-person interviews were performed, and obtained information on demographic and lifestyle characteristics, medical history and obstetrical history. For powder use on sanitary napkins and deodorant spray, investigators recorded the total number of months of use. For the use of powder on the perineum after bathing, only intervals of at least one year when powder was usually used was recorded. Women were also asked to report the “types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The extent of exposure to perineal powder after bathing was assessed as lifetime duration of use . . . and as the estimated lifetime number of applications.” There was no statistically significant increase in the risk of ovarian cancer for using powder after bathing (OR: 1.27; 95% CI: 0.97-1.66) after adjusting for age, calendar year of diagnosis/reference date, county of residence, number of full-term births and duration of hormonal contraception.

Kurta et al.⁴⁷ in 2012 conducted a case-control study using data from the Hormones and Ovarian Cancer Prediction (HOPE) study. Cases were residents of Western Pennsylvania, Eastern Ohio and Western New York State and had histologically confirmed ovarian, peritoneal or fallopian tube cancers diagnosed between 2003 and 2008. Controls were frequency matched and identified through random digit dialing. Trained interviewers collected questionnaire data that included medical history and information about lifestyle. “Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps.” Perineal talc use was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.40; 95% CI: 1.16-1.69) after adjusting for age and education.

⁴⁶ Rosenblatt et al., *Genital powder exposure and the risk of epithelial ovarian cancer*. (2011) 22 Cancer Causes Control 737.

⁴⁷ Kurta et al., *Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case-Control Study*. (2012) 21(8) Cancer Epidemiol Biomarkers Prev. 1282.

Terry et al.⁴⁸ in 2013 reported on a pooled analysis of case-control studies using data from the Ovarian Cancer Association Consortium. Investigators used data from eight case-control studies and included 8,525 cases of ovarian, fallopian tube or peritoneal cancer and 9,859 controls. Genital powder use was defined as “any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area.” Criteria for regular use varied between studies from “ever use” to “one year or longer.” “Women who reported both genital and non-genital powder use were classified as genital users.” Genital use of powder was associated with a statistically significant increase in risk of ovarian cancer when compared with no powder use (OR: 1.24; 95% CI: 1.15-1.33) after adjusting for age, oral contraceptive use, parity, tubal ligation history, BMI and race/ethnicity.

Wu et al.⁴⁹ in 2015 reported a case-control study of women with newly diagnosed histologically confirmed invasive epithelial ovarian cancer identified through the Cancer Surveillance Program. Cases were non-Hispanic white, Hispanic, or African American women aged 18 to 74 diagnosed between 2003 and 2008. In-person interviews were conducted using questionnaires, which included questions on demographics, lifestyle, medical history, family history and genital talc use. Results are based on pooling of four case-control studies in Los Angeles County investigating invasive epithelial ovarian cancer. Genital talc use was associated with a statistically significant increase in risk for invasive ovarian cancer in all study participants (OR: 1.46; 95% CI: 1.27-1.69); non-Hispanic whites (OR: 1.41; 95% CI: 1.21-1.67) and Hispanics (OR: 1.77; 95% CI: 1.20-2.62), but not in African Americans (OR: 1.56; 95% CI: 0.80-3.04). Every five years of talc use was also associated with a statistically significant increase in risk for invasive ovarian cancer in non-Hispanic whites (OR: 1.14; 95% CI: 1.08-1.21) and Hispanics (OR: 1.18; 95% CI: 1.02-1.36), but not in African Americans (OR: 1.15; 95% CI: 0.90-1.47). Estimates were adjusted for menopausal status, age at menarche, hormone therapy use, BMI, income, education, parity, oral contraceptive use, tubal ligation, endometriosis and family history of ovarian cancer.

Schildkraut et al.⁵⁰ in 2016 reported a case-control study of women enrolled in the African American Cancer Epidemiology Study from 11 locations in the United States. Cases included African American women aged 20 to 79 with newly diagnosed ovarian cancer. Controls were African American women who were identified through random digit dialing. Participants completed a baseline telephone interview, which includes questions on demographics, medical history and information on lifestyle. “[P]articipants were asked whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Participants were considered ‘regular users’ if they reported using any of these powders at least one time per month for at least six months, and ‘never users’ if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether

⁴⁸ Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*. (2013) 6(8) *Cancer Prev Res* 811.

⁴⁹ Wu et al., *African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*. (2015) 24(7) *Cancer Epidemiol Biomarkers Prev*. 1094 (“Wu 2015”).

⁵⁰ Schildkraut (2016).

they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or nongenital areas.” There was a statistically significant increase in the risk of ovarian cancer with any genital use of powder (OR: 1.44; 95% CI: 1.11-1.86) after adjusting for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of oral contraceptive use, first-degree family history of breast or ovarian cancer and interview year. In addition, as discussed above, when investigators stratified by the interview date, there was no statistically significant association between ovarian cancer and any genital use of body powder if the interview date was before 2014 (OR: 1.19; 95% CI: 0.87-1.63), but if the interview date was after 2014, there was a statistically significant increase in risk of ovarian cancer with any genital use of body powder (OR: 2.91; 95% CI: 1.70-4.97), after adjusting for the same potential confounders.

Cramer et al.⁵¹ in 2016 reported a pooled analysis of case-control studies of women residing in Eastern Massachusetts and New Hampshire diagnosed with ovarian cancer between the ages of 18 and 80 using data from the NHS and several sites from the Ovarian Cancer Association Consortium. Controls were identified through random digit dialing. Participants “were asked whether they ‘regularly’ or ‘at least monthly’ applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital-rectal area. Additional details included type of powder, age begun, years used, and applications per month. Lifetime exposure was estimated by multiplying frequency of application per month by months used.” This was divided by 360 to yield talc-years, which were divided into separate quartiles for dose-response analysis. Any genital powder use was associated with a statistically significant increase in the risk of ovarian cancer (OR: 1.33; 95% CI: 1.16-1.52) after adjusting for reference age, study center and study phase. There was no clear pattern suggesting a dose-response effect, with a random sine wave pattern with increasing risk, then decreasing risk, then increasing risk with total genital talc applications.

D. Cohort Studies

Gertig et al.⁵² reported the relationship between perineal talc use and ovarian cancer using participants from the NHS. This is a prospective study of 121,700 registered nurses in the United States who were ages 30-55 years at enrollment in 1976. Talc exposure was not evaluated when the study began, but questions regarding talc exposure were added in 1982. 78,630 women completed the questions regarding talc at baseline and formed the cohort for analysis and were followed for 14 years (1982-1996). There were 307 women who were subsequently diagnosed with ovarian cancer. After adjusting for confounders, no statistically significant association was found with ever talc use, with a relative risk for ovarian cancer of 1.09 (95% CI: 0.86-1.37) when compared to never talc use. Similarly, no statistically significant association was found with daily talc use, with a relative risk of 1.12 (95% CI: 0.82-1.55) when compared with never talc after adjusting for age, parity, duration of oral contraceptive use, BMI, tubal ligation, smoking status and postmenopausal hormone use. There was an increase in risk of invasive serous ovarian cancer, with a relative risk of

⁵¹ Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*. (2016) 27(3) *Epidemiology* 334.

⁵² Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 *J. Nat. Cancer Inst.* 249.

1.40 (95% CI: 1.02-1.91) among ever talc users when compared to never talc users after adjusting for the same potential confounders.

Gates et al.⁵³ examined the association between ovarian cancer risk factors and ovarian cancer by histological subtype in the NHS and Nurses' Health Study II (NHSII). This prospective study included 221,866 women who completed baseline and biennial follow-up providing information on lifestyle factors and disease diagnoses. Follow-up was longer than the Gertig study and was 24 years in the NHS (1982-2006) and six years in the NHSII. There were 924 women who subsequently developed ovarian cancer and 721 cases with the histologies of interest (496 serous invasive, 139 endometrioid, 86 mucinous). Information on regular talc use was collected in 1982 and available for NHS participants only (108,870 women). No statistically significant increases in risk were found between talc used greater than once weekly with all epithelial (RR: 1.06; 95% CI: 0.89-1.28), serous invasive (RR: 1.06; 95% CI: 0.84-1.35), endometrioid (RR: 1.06; 95% CI: 0.66-1.69), or mucinous (RR: 1.5; 95% CI: 0.84-2.66) ovarian cancer when compared with less than once weekly talc use after adjusting for age, BMI, activity level, parity, breastfeeding, oral contraceptive use, tubal ligation, age at menopause, estrogen use, menopause status, smoking status and family history of breast or ovarian cancer.

Houghton et al.⁵⁴ assessed the perineal powder use and the risk of ovarian cancer prospectively in the Women's Health Initiative observational cohort, which enrolled postmenopausal women aged 50-79 from 40 clinical centers across the United States from 1993 to 1998 through 2012. Participants completed annual questionnaires to obtain information on risk factors and outcomes, including ovarian cancer. Perineal powder was assessed via self-report at baseline by asking participants if they had ever used powder on their private parts (genital areas). Those who answered yes were asked questions regarding duration of use. Participants were also asked about use with diaphragms and sanitary napkins or pads. There were 61,576 women who completed baseline questionnaires and followed for a mean 12.4 years. There were 429 women who subsequently developed ovarian cancer. No statistically significant increase in risk of ovarian cancer between ever powder use on genitals (HR: 1.12; 95% CI: 0.92-1.36) and never powder use on genitals was found after adjusting for age, race, duration of oral contraceptive use, duration of hormone replacement therapy, family history, age at last birth, BMI, smoking status, tubal ligation and parity. There was also no statistically significant increase in risk from duration of use between talc use greater than 10 years (RR: 0.98; 95% CI: 0.75-1.29) or greater than 20 years (RR: 1.10; 95% CI: 0.82-1.48) when compared with never talc use after adjusting for the same potential confounders. Similarly, no statistically significant increase in risk was found for all serous (RR: 1.16; 95% CI: 0.88-1.53), serous invasive (RR: 1.13; 95% CI: 0.84-1.51), mucinous (RR: 1.03; 95% CI: 0.47-2.27), or endometrioid (RR: 1.29; 95% CI: 0.64-2.61) ovarian cancer between ever talc use and never talc use after adjusting for the same potential confounders.

⁵³ Gates et al., *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype*. (2010) 171 Am. J. Epidemiology 45.

⁵⁴ Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*. (2014) 106(9) J Nat. Cancer Inst.

Gonzalez et al.⁵⁵ evaluated the effect of douching and talc use on the risk of ovarian cancer prospectively in the Sister Study, which enrolled women aged 35 to 74 who had never had breast cancer and who had a sister or half-sister diagnosed with breast cancer in the United States and Puerto Rico from 2003 to 2009 through 2014. Participants completed computer-assisted telephone interviews, which included questions about lifestyle factors and health conditions. Participants also completed a self-administered questionnaire about personal products used in the 12 months prior to enrollment, which included questions about frequency of douching as well as talc use, method of talc use, and frequency of talc use. There were 50,884 women who completed questionnaires and, after excluding participants who had bilateral oophorectomies or ovarian cancer before enrollment or who had no follow-up information, 41,654 women were followed for a median of 6.6 years. There was no statistically significant increased risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use during the 12 months prior to the study when compared with never talc use after adjusting for race, BMI, parity, duration of oral contraceptive use, baseline menopausal status and tubal ligation. There was, however, a statistically significant increase in risk of ovarian cancer (HR: 1.9; 95% CI: 1.2-2.9) with douching/no talc use when compared with neither use as well as an increased risk of ovarian cancer with douching in the past 12 months (HR: 1.8; 95% CI: 1.2-2.8) when compared with never douching after adjustment for the same potential confounders. This study highlights the potential for douching to be a confounder in previous investigations, and all but one study failed to control for the potential confounding effect of douching and risk of ovarian cancer.

E. Summary Of Observational Studies

Evaluating the association between talc use and ovarian cancer in case-control studies poses several challenges that require attention. The assessment of exposure is difficult because it is solely based on self-report. Talc purchasing and use are not documented in the medical records or available in pharmacy records. As there is no reliable method of confirming talc usage, the accuracy and validity of these studies even under perfect circumstances can be dramatically affected by reporting bias. Additionally, the quantification of talc exposure is very difficult and may be impossible to verify accurately. Powders have varying amounts of talc and can be applied by various methods, leading to more or less exposure. There is no standardized dose/amount that is used, and there is no standard quantification method with verification that has been universally employed among the studies in the medical literature. Various studies collected information on the reported use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, not genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on diaphragms, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. As such, there are no case-control or cohort epidemiologic studies or meta-analyses that have investigated the effect of a standardized amount of talc usage or a standardized method of use to ensure consistency of the assessment of exposure. In addition, only a few epidemiologic studies have found any dose-response relationship between genital talc use and ovarian cancer.

⁵⁵ Gonzalez (2016).

Furthermore, as in all case-control studies, recall bias is also of great concern. This arises from the phenomenon that cases are more likely than controls to think about and remember past exposures. Recall bias leads to differential misclassification of exposure and a falsely elevated estimate of risk between talc exposure and ovarian cancer. This is especially important if an exposure such as talc appeared in the news or was discussed in the public arena as having a possible causative association with ovarian cancer. There is evidence to suggest that hospital-based case-control studies are less likely to be subject to recall bias than population-based case-control studies because the degree to which study subjects think about possible past exposure is more similar (given that both cases and controls are being hospitalized).⁵⁶

In general, cohort studies provide more evidence for a causal relationship between exposure and outcome and can often study many exposure-outcome relationships with less chance for bias and confounding than case-control studies if the design, conduct, data collection and analysis are proper. However, cohort study designs also remain susceptible to certain types of bias and confounding, and cohort studies are often very expensive, take a long time to conduct, and may be difficult to perform, especially if the outcome of interest is rare.

Plaintiffs' epidemiologists repeatedly downplay the results of the four relevant cohort studies. Dr. McTiernan, for example, has the opinion that there are a number of "serious limitations" in the cohort studies, including that they were not specifically designed to investigate the relationship between talc use and ovarian cancer, but rather examined a number of different outcomes.⁵⁷ This point is irrelevant as cohort studies are designed specifically to have the ability to investigate many exposure-outcome relationships, even if the cohort study was not specifically designed to look at the exposure-outcome relationship of interest. Dr. McTiernan also criticizes the cohort studies on other grounds – that they did not obtain detailed lifetime histories of talcum powder use and therefore could not measure dose-response; that the sample sizes were too small to detect a relative risk like 1.24; and that the latency period of ovarian cancer makes these studies "not likely reflective of risk from exposure to talcum powder products."⁵⁸ But as just explained, no type of study in this context can provide an accurate measure of dose-response due to the problems inherent in relying on study participants' subjective assessments regarding the amount of talcum powder they use, and as I elaborate in part VIII.A below, Dr. McTiernan's criticisms with respect to latency and sample size are speculative and wrong. All of this suggests that Dr. McTiernan's criticisms reflect her own bias. While cohort studies also have their own limitations like any other study design, the focused criticism of cohort studies by plaintiffs' epidemiologists, even though they are generally considered more reliable than case-control studies, suggests a biased approach to their analyses.

⁵⁶ Oleckno, *Epidemiology: Concepts and Methods*. (2008) at 207; Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Severe Childhood Diseases?* (2003) 157(2) *Am J Epidemiol* 176.

⁵⁷ McTiernan Report 46.

⁵⁸ *Id.* at 46-47.

F. Meta-Analysis

Gross et al.⁵⁹ in 1995 reviewed nine case-control studies (all previously described above) and one cohort study to evaluate the association between talc and ovarian cancer. The authors combined the results of seven studies and found an increase in risk of ovarian cancer (RR: 1.20; 95% CI: 1.01-1.44) with any talc exposure, and combined the results of five studies and, after adjustment, found an increase in risk of ovarian cancer (RR: 1.29; 95% CI: 1.02-1.63). Unfortunately, there is little detail provided regarding the methods used to identify, evaluate and analyze the studies, making the interpretation of this investigation challenging and problematic. In addition, all of the limitations described above with respect to the included case-control studies remain inherent within this investigation.

Huncharek et al.⁶⁰ in 2003 evaluated 15 case-control studies (all previously described above) and one cohort study using a predefined technique for literature search, study inclusion and analysis. The study included data from 11,933 subjects and pooling all subjects demonstrated a summary OR of 1.33 (95% CI: 1.16-1.45) for ovarian cancer with being exposed to never versus ever talc, none versus any talc and never versus any talc. Seven studies analyzed together yielded an inverse relationship between duration of exposure and ovarian cancer, with low-exposure groups having a higher risk and high-exposure groups having a lower risk, demonstrating a lack of clear dose-response. Hospital-based case-control studies demonstrated no significant relationship between talc use and risk of ovarian cancer (RR: 1.19; 95% CI: 0.99-1.41), while population-based case-control studies showed an increased risk of ovarian cancer with talc use (RR: 1.38; 95% CI: 1.25-1.52). As mentioned above, the limitations of the previously described case-control studies remain inherent within this review. Furthermore, differences in recall bias between hospital-based and population-based case-control studies provide one possible explanation for differences found between the two different study designs.

Huncharek et al.⁶¹ in 2007 evaluated nine case-control studies (all previously described above) investigating the association between talc via dusting of contraceptive diaphragms and ovarian cancer in 2,281 cases of ovarian cancer and 3,608 controls using a predefined technique for literature search, study inclusion and analysis. Pooling all subjects demonstrated no significant risk of ovarian cancer with being exposed to talc via dusting of contraceptive diaphragms (OR 1.03; 95% CI: 0.80-1.37). One included case-control study did not explicitly provide data on talc use via contraceptive diaphragms, and without data from this study, the resultant OR was 1.12 (95% CI: 0.84-1.48).⁶²

⁵⁹ Gross & Berg, *A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer*. (1995) 5(2) J Expo Anal Environ Epidemiol. 181.

⁶⁰ Huncharek et al., *Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies*. (2003) 23 Anticancer Res. 1955.

⁶¹ Huncharek et al., *Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies*. (2007) 18 Eur J Cancer Prev 422.

⁶² Dr. Zambelli-Weiner has criticized the Huncharek studies and did indeed find some errors in them. However, her analysis did not show that any errors materially affected the conclusions of these studies.

Langseth et al.⁶³ in 2008 reported on a meta-analysis of 20 case-control studies and make reference to one cohort study. Results were separated into 14 population-based case-control studies and six hospital-based case-control studies. The investigators state that the cohort study showed “no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined,” although the results were not shown. The hospital-based case-control studies reported a pooled odds ratio of 1.12 (95% CI: 0.92-1.36) and the population-based case-control studies reported a pooled odds ratio of 1.40 (95% CI: 1.29-1.52). The combined OR from all case-control studies using a fixed effects model was 1.35 (95% CI: 1.26-1.46). This meta-analysis reflects some methodological weaknesses, including the fact that there is no report of a literature search strategy and no structured review of the literature for eligible studies.

Berge et al.⁶⁴ in 2018 reported on a meta-analysis of 27 studies, which included 24 case-control studies and three cohort studies. The authors reported a “small increased risk” with a summary relative risk of 1.22 (95% CI: 1.13-1.30) for ever talc use and ovarian cancer, but found that the cohort studies did not show an association (RR 1.02 (95% CI: 0.85-1.20)). The investigators demonstrated that given the total number of exposed and unexposed cases of ovarian cancer, the statistical power of the cohort studies to detect a relative risk difference of 1.25 was 0.99, which matched that of the case-control studies, and thus rejected inadequate power as an explanation for the lack of an association between talc exposure and ovarian cancer in the cohort studies and the heterogeneity between study designs. The study found a “weak trend in RR with duration and frequency of genital talc use,” but cautioned that this analysis was based on few studies and that the “modest association between both duration and frequency of use of talc may reflect a true relationship, or recall bias or confounding.” The authors noted that several aspects of their analysis, including heterogeneity between case-control and cohort studies, did “not support a causal interpretation of the association.”

Penninkilampi et al.⁶⁵ in 2018 reported on a meta-analysis of 24 case-control studies and three cohort studies. The study reported a summary odds ratio of 1.31 (95% CI: 1.24, 1.39) for any talc use and ovarian cancer, but this association was not present in cohort studies (OR 1.06 (95% CI: 0.90-1.25)). Although the study reported a statistically significant association in the cohort studies for serous invasive ovarian cancer (OR 1.25 (95% CI: 1.01, 1.55)), it excluded the 2010 Gates study from its analysis. The study further found that more than 3,600 lifetime talc applications “were slightly more associated with ovarian cancer than” fewer than 3,600 lifetime applications (odds ratios of 1.42 and 1.32, respectively), but noted that these data came from case-control studies and were therefore “prone to recall bias” (which the study observed could be particularly problematic due to recent media coverage of talc lawsuits). It also observed that the “mechanism by which perineal talc use may increase the risk of ovarian cancer is uncertain,” and in particular that use of NSAIDs “is not inversely associated with the incidence of ovarian cancer, as may be

⁶³ Langseth et al., *Perineal use of talc and risk of ovarian cancer*. (2008) 62 J Epidemiol Community Health 358.

⁶⁴ Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis*. (2018) 27 Eur J Cancer Prev 248.

⁶⁵ Penninkilampi and Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*. (2018) 29(1) Epidemiology 41.

expected if the etiology was related to chronic inflammation.” The authors cited the “substantial need for further research on a potential mechanism” as one reason why a causal relationship could not be established with any certainty.

In summary, the published meta-analyses have been of varying quality and in general observed a weak association (odds ratio roughly 1.3) between talc use and ovarian cancer. However, as the meta-analyses have noted, the observed increased risk is restricted entirely to case-control studies and may be a result of bias and/or confounding. Although different studies employ different techniques to attempt to adjust for these issues, meta-analyses are only as good as their underlying studies, and the fact that the meta-analyses themselves combine studies that used different adjustment approaches can exacerbate issues regarding overall reliability.

VII. ANALYSIS OF STUDIES

It is my opinion that there is insufficient evidence to support a causal association between exposure to talc and risk of ovarian cancer based on the body of available epidemiologic observational studies that have been performed and reported in the literature. While there is no single method for undertaking a causal assessment based on epidemiology, the criteria formulated by Austin Bradford Hill are often used and are considered the gold standard for evaluating causation once an association has been identified. These include: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimentation and analogy.⁶⁶ While Bradford Hill suggests nine different viewpoints to consider in a careful examination of the association between exposure and outcome before concluding that a causal relationship exists, it is important to understand that none of his concepts provide unquestionable evidence for or against a causative relationship and none is required as essential or absolutely necessary. They can simply help to provide a framework to guide epidemiologists to decide whether or not there is another more likely way of explaining the association, including non-causal explanations for the results of individual studies. These other explanations can come from bias, confounding and/or random error (as discussed above), can lead to risk estimates that are falsely higher or lower than actual risk and can even lead to conclusions that an exposure causes disease when it does not.

Even before starting such an analysis, however, one should examine whether the epidemiologic literature establishes a true association – the fundamental predicate of a Bradford Hill analysis. As Hill noted in his seminal article setting forth his epidemiologic approach, before evaluating causation, studies must “reveal an association between two variables, *perfectly clear-cut and beyond what we would care to attribute to the play of chance*.”⁶⁷ As I discuss further below, this requirement is likely not satisfied here because we are not presented with a “clear cut” association.

A number of the Hill factors further weigh decidedly against a causal finding in this instance. In particular, and as detailed in this section, lack of consistent results among studies, lack of reliable assessment of exposure to talc, lack of a dose-response relationship

⁶⁶ Hill, *Environment and disease: association or causation?* (1965) 58 Proc Royal Soc Med. 295.

⁶⁷ *Id.*

and lack of strength of association all contribute to my opinion that there is a lack of reliable evidence to conclude that exposure to talc increases the risk of ovarian cancer.

A. Lack Of Consistency Between Studies

One of the most striking aspects of the studies is their inconsistency.

Some studies demonstrate an association between talc use and ovarian cancer, while others do not. As set forth in the table below, there are seven hospital-based case-control studies that consistently demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. There are four cohort studies that also consistently demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. There are 26 population-based case-control studies that demonstrate inconsistent results, with some studies demonstrating a statistically significant association between exposure to talc and risk of ovarian cancer, while others demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. This lack of consistency in finding a statistically significant association between talc use and risk of ovarian cancer likely arises from several factors. The studies use varying questionnaires, describe varying self-reported assessments of talc exposure and varying self-reported assessments of frequency and duration of talc use, and apply no adjustment or varying levels of adjustment for potential confounders. Finally, each one of these observational studies has limitations (recall bias and confounding in case-control studies; lack of repeated measure of exposure in cohort studies). The consistency of effect between hospital-based case-control studies and the cohort studies is somewhat assuring and the heterogeneity among population-based case-control studies weigh against finding a causal relationship between exposure and outcome. In addition, even though the methods for at least two of the reported meta-analyses were relatively robust, the studies that were used in all of the meta-analyses were of limited quality.

B. Lack Of Reliable Assessment Of Talc Exposure

In all of the studies investigating the possible causal association between talc and ovarian cancer, assessment of talc exposure relies on self-report. Talc use is not documented in a medical record or in a pharmacy record in order to confirm, or at least verify, self-reported use. This has a substantial potential to lead to recall and reporting bias, in particular in case-control studies, although this type of bias may also be present in cohort studies. Furthermore, self-reported exposures were obtained from responses to questionnaires on the use of talc or talc products, including: use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, non-genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on diaphragms, “genital fiber use”, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/ perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. Varying amounts of talc exist within different powders, varied methods can be used to apply talc either by spray or by powder, varying amounts may be applied on diaphragms, and the amount applied may be very different depending on the method of application and the person applying it. Questions arise, such as: How much talc is used in dusting? How much talc is used in the perineum? How much

talc is used after bathing only, etc.? In addition, there are no observational studies or meta-analyses that have investigated the effect of a standardized amount of talc usage or a standardized method of use to ensure consistency of the assessment of exposure. As an epidemiologist, I find this lack of ability to quantify a dose to be a gaping hole in the exposure-outcome relationship and a tremendous limitation in all of the epidemiologic studies evaluating talc and risk of ovarian cancer.

C. Lack Of A Dose-Response To Talc Exposure

There have been very few case-control studies and no cohort studies that have reported a dose-response relationship between talc exposure and risk of ovarian cancer; and measures of dose-response generally have varied widely among studies.

Dose-response curves may increase with increasing exposure (i.e., increased risk of heart disease with increasing level of cholesterol) and decrease with increasing exposure (i.e., decreased risk of heart disease with increased doses of cholesterol lowering agent). Typically, a dose-response curve that depicts an increased risk would demonstrate increasing risk with increasing quantity of exposure, increasing frequency of exposure, increasing duration of exposure or a combination. When the curve is concave, convex or has a haphazard random shape, that is a red flag to epidemiologists. Studies that have evaluated the potential for dose-response have found: (1) random or “sine wave” (up and down) risk⁶⁸; (2) convex (up then down) risk⁶⁹; (3) concave (down then up) risk⁷⁰; and (4) even decreasing risk⁷¹ with either increasing frequency or duration of talc use. Studies by Wu⁷² and Cramer⁷³ demonstrated increasing risk of ovarian cancer with increasing frequency and duration of reported talc use, but not all cut-offs were statistically significant. Only one study⁷⁴ demonstrated a statistically significant association between duration of reported talc use (per five years of reported genital talc use) and risk of ovarian cancer in Hispanics (OR: 1.18; 95% CI: 1.02-1.36) and non-Hispanic whites (OR: 1.14; 95% CI: 1.08-1.21).

In sum, the vast majority of both case-control and cohort studies demonstrate no statistically significant dose-response relationship between talc use and risk of ovarian cancer.

D. Lack Of Strength Of Association

Another indicator of causality is strength of association.

⁶⁸ Booth (1989); Wong (1999); Cook (1997); Mills (2004); Merritt (2008); Gertig (2000).

⁶⁹ Cramer (1999); Chang (1997); Cramer (2016); Rosenblatt (2011); Houghton (2014).

⁷⁰ Whittemore (1988); Gates (2008).

⁷¹ Hartge (1983).

⁷² Wu (2009).

⁷³ Cramer (2016).

⁷⁴ Wu (2015).

Relative risk and odds ratios are two measures of strength of association. The higher the relative risk or odds ratio, the greater the likelihood that the relationship is causal. For instance, the International Primary Pulmonary Hypertension Study was a case-control study where cases were defined as patients with pulmonary hypertension without a known reason.⁷⁵ Controls were randomly selected from lists of consecutive patients seen by the same general practitioner. Each participant went through a face-to-face interview and was asked about demographics, medical and surgical history as well as medication history. Use of appetite suppressants was associated with a statistically significant increase in risk of pulmonary hypertension (OR: 6.3; 95% CI: 3.0-13.2) after adjusting for systemic hypertension, use of cocaine or intravenous drugs, smoking status, BMI, weight loss behavior, use of thyroid extracts and possible exposure to anorexic agents. The odds ratio in this study was found to be 6.3, and with a relative risk this high it is unlikely that any other factor could be the cause of the association.

The higher the relative risk or odds ratio, the less likely other factors can explain the association. Similarly, for relative risks or odds ratios that are lower, it is important to understand that there may be factors other than the exposure of interest that can explain the association. Rosenblatt (1998)⁷⁶ found a statistically significant association between women who had ever douched and those who used powder in the perineal area (OR: 2.9; 95% CI: 1.6-5.1). Gonzalez et al.⁷⁷ as described above evaluated the effect of douching and talc use on the risk of ovarian cancer prospectively in the Sister Study. Results demonstrated no statistically significant increased risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use when compared with never talc use after adjusting for confounders. However, there was a statistically significant increase in risk of ovarian cancer (HR: 1.9; 95% CI: 1.2-2.9) with douching/no talc use when compared with neither use as well as a statistically significant increase in risk of ovarian cancer with douching in the past 12 months (HR: 1.84; 95% CI: 1.2-2.8) when compared with never douching. As previous studies (except for Harlow et al. (1992)) did not account for douching, the relatively weak statistically significant associations could potentially be explained by confounding. One explanation could be that since talc users are more likely to douche and douching appears to increase risk of ovarian cancer, previous studies may not have captured the correct exposure (douching) in the causal pathway and mistakenly concluded talc to be the exposure that increased risk of ovarian cancer instead of douching. Similarly, it is also possible that the relatively weak yet statistically significant associations seen in some of the case-control studies could be explained by other potential confounders that were only considered in some of the studies or that have not yet even been identified.

In summary, based on evidence in the literature and the lack of consistency across studies, the lack of a reliable assessment of actual talc exposure, the lack of a significant dose-response to talc exposure, and a weak strength of association between a poorly characterized exposure to talc and risk of ovarian cancer, it is impossible to conclude that talc exposure increases the risk of ovarian cancer.

⁷⁵ Abenham et al., *Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension*. (1996) 335(9) N Engl J Med 609.

⁷⁶ Rosenblatt (1998).

⁷⁷ Gonzalez (2016).

Author	Odds Ratio/Relative Risk/Hazard Ratio	95% CI	Statistically Significant Association?
Hospital-based case-control studies			
Hartge et al. (1983)	0.70	0.04-1.10	No
Whittemore et al. (1988)	1.45	0.81-2.60	No
Booth et al. (1989)	1.30	0.80-1.90	No
Rosenblatt et al. (1992)	1.70	0.70-3.90	No
Tzonou et al. (1993)	1.05	0.28-3.98	No
Hartge and Stewart (1994)	0.30 (5-9 years of talc exposure) 0.50 (10+ years)	0.10-1.40 0.20-1.50	No
Wong et al. (1999)	1.13	0.88-1.44	No
Population-based case-control studies			
Cramer et al. (1982)	1.92	1.27-2.89	Weak
Harlow and Weiss. (1989)	1.10	0.70-2.10	No
Harlow et al. (1992)	1.50	1.00-2.10	Weak
Chen et al. (1992)	3.90	0.90-10.6	No
Cramer and Xu (1995)	1.60	1.20-2.10	Weak
Purdie et al. (1995)	1.27	1.04-1.54	Weak
Green et al. (1997)	1.30	1.10-1.60	Weak
Shushan et al. (1996)	1.97	1.06-3.66	Weak
Chang and Risch (1997)	1.42	1.08-1.86	Weak
Cook et al. (1997)	1.60	0.90-2.80	No
Godard et al. (1998)	2.49	0.94-6.58	No
Cramer et al. (1999)	1.60	1.18-2.15	Weak
Ness et al. (2000)	1.50	1.10-2.00	Weak
Mills et al. (2004)	1.37	1.02-1.85	Weak
Pike et al. (2004)	1.60	1.18-2.18	Weak
Jordan et al. (2007)	1.00	0.40-2.10	No
Gates et al. (2008)	1.36	1.14-1.63	Weak
Merritt et al. (2008)	1.17	1.01-1.36	Weak
Moorman et al. (2009)	Afr. Am.: 1.19 Caucasian: 1.04	Afr. Am: 0.68-2.09 Caucasian: 0.82-1.33	No
Wu et al. (2009)	1.53	1.13-2.09	Weak
Rosenblatt. (2011)	1.27	0.97-1.66	No
Kurta et al. (2012)	1.40	1.16-1.69	Weak
Wu et al. (2015)	1.46	1.27-1.69	Weak
Schildkraut et al. (2016)	1.44	1.11-1.86	Weak
Pooled case-control studies			
Terry et al. (2013)	1.24	1.15-1.33	Weak

Author	Odds Ratio/Relative Risk/Hazard Ratio	95% CI	Statistically Significant Association?
Cramer et al. (2016)	1.33	1.16-1.52	Weak
Cohort studies			
Gertig et al. (2000)	1.09	0.86-1.37	No
Gates et al. (2010)	1.06	0.89-1.28	No
Houghton et al. (2014)	1.12	0.92-1.36	No
Gonzalez et al. (2016)	0.73	0.44-1.20	No

VIII. METHODOLOGICAL FLAWS IN PLAINTIFFS' EXPERTS' EPIDEMIOLOGY-BASED OPINIONS

I was asked to address whether the causation analyses set forth in the expert reports of plaintiffs' epidemiology experts were conducted in a scientifically reliable manner. As set forth below, I have concluded that there are several significant methodological flaws that are prevalent in multiple plaintiffs' experts' reports, rendering their analyses unreliable.

A. Disregard For The Hierarchy Of Evidence

The hierarchy of evidence is well-established within the scientific community.⁷⁸ Consistent with that hierarchy, epidemiologists consider meta-analyses of multiple randomized clinical trials, followed by individual randomized clinical trials, as the strongest evidence to support a causal relationship between an exposure and an outcome. These are followed by the observational designs, with cohort studies, case-control studies, and cross-sectional studies in descending order also providing potential evidence for a causal association between exposure and outcome. The lowest quality of evidence comes from case reports, case series and other descriptive studies. As a general rule, lower-quality studies provide less information on whether a causal relationship exists than studies of higher quality.

Although this hierarchy should not be indiscriminately applied to all research questions and studies, an epidemiologist should provide sound scientific justifications for departing from these well-established norms. For example, a poorly designed and conducted meta-analysis or randomized clinical trial may provide less evidence than a well-designed and conducted cohort or case-control study.

A number of plaintiffs' epidemiologists ignore the well-established hierarchy of evidence in their reviews of the relevant human studies, either by treating all studies equally or, even more troublingly, placing an inappropriate amount of weight on case-control studies that they claim demonstrate a weak association between talc use and ovarian cancer, while ignoring stronger, better designed cohort studies that do not show any association and also better capture the temporal nature that must exist to demonstrate a causal relationship

⁷⁸ Nat. Health & Medical Res. Council, *NHMRC Levels of Evidence and Grades for Recommendations for Developers of Clinical Practice Guidelines* (2009).

between exposure and outcome. For example, Dr. Moorman states the following in her report:

As I evaluated individual epidemiologic studies (case-control and cohort studies) that described the risk for ovarian cancer associated with talc use, I did not weight one design more heavily than the other because there are advantages and disadvantages to each design for evaluating talc as a cause of ovarian cancer.⁷⁹

Likewise, Dr. McTiernan states in her report that “all” studies provide evidence of causal effect.⁸⁰ When asked at her deposition about the hierarchy of scientific evidence, Dr. McTiernan testified that she was “not sure what hierarchy” the questioner was referring to and that, in any event, “depending on the question, one type of study could be preferable to another, but in general all of the studies provide information, and we look at the totality of evidence.”⁸¹ When I teach students about study design in epidemiology, this is exactly what I tell them *not* to do. When evaluating whether causality can be demonstrated from a particular study or series of studies, it is essential to evaluate the strengths and potential weaknesses of each individual study. Because case-control studies are more easily subject to biases and confounding factors and can often not fully capture the temporal relationship between exposure and outcome, as discussed in detail below, they are often less reliable than cohort studies.

Even more problematic than treating all studies the same is plaintiffs’ experts’ tendency to place *more* emphasis on case-control studies than higher-quality cohort studies, despite their limitations. For example, despite her disclaimer of adherence to any hierarchy of evidence, Dr. McTiernan does apply a hierarchy of her own, suggesting that case-control studies are preferable in situations where an exposure is “very difficult to measure and which can change over time.”⁸² While I agree with her that case-control studies are often “easier” when an exposure may be “difficult to measure,”⁸³ a poor-quality case-control study does not provide higher quality data due to limitations in design. Furthermore, case-control studies, as mentioned above, can be subject to bias and confounding, even when they are well designed. Even though case-control studies sometimes may be “easier” to conduct, the temporal relationship between exposure and outcome is often more difficult to establish because ascertainment of the exposure is done after the outcome. Finally, it is often extremely difficult for a case-control study design to accurately investigate an exposure that changes over time and a cohort design will more likely be able to investigate time varying exposures than a case-control study design. Dr. McTiernan’s suggestion therefore is illogical, and in my opinion, is not supported by any science.

⁷⁹ Moorman Report 10.

⁸⁰ McTiernan Report 18.

⁸¹ McTiernan Deposition 118.

⁸² McTiernan Deposition 117.

⁸³ *Id.*

Dr. McTiernan has also criticized the multiple cohort studies finding no association between talc use and ovarian cancer on the ground that those studies involved an “insufficient number of cases . . . to find a statistically significant result.”⁸⁴ Dr. McTiernan’s criticism seems to be that, because ovarian cancer has a low incidence rate – and so few study participants developed the disease in both the study and control populations – the studies cannot rule out the possibility of a link between talc use and ovarian cancer. This position is incorrect.

The first problem with Dr. McTiernan’s criticism is that her focus on the low overall incidence of ovarian cancer in the population is misplaced. Incidence rates reported by the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program are estimated rates for *all* women. These rates may change from year to year, and rates may be different for different age groups and races as reported by SEER.⁸⁵ Observational studies do not study the population at large, but rather a subset of the population (i.e., study participants). And the incidence of ovarian cancer in the population enrolled in the cohort studies, including Gonzalez (2016) (41,654 women),⁸⁶ Houghton (2014) (61,576 women),⁸⁷ and Gates (2010)/Gertig (2000) (108,870 women),⁸⁸ was higher than in the general population, with 429 cases among 68,435 participants who reported exposure to talc, and 943 cases among 141,345 participants who reported no exposure to talc. It is not surprising that the incidence rates of ovarian cancer in the cohort studies are much higher than the reported rates for all females by the SEER Program because the cohort studies may include women who are in general at higher risk of developing ovarian cancer (i.e., older age, family history of cancer etc.).

A higher incidence of disease in the study population means that the number of participants needed to detect true risk is decreased – i.e., smaller sample sizes can detect the same amount of risk. Thus, because the cohort studies involve women who likely have a higher risk of ovarian cancer than the general population as reported by SEER, the study sample sizes needed to detect a given difference in risk between groups will be smaller. (This is why epidemiologists study higher-risk groups for less-common disease.) Specifically, using the Berge study’s meta-analysis of cohort studies,⁸⁹ which concluded that combined cohort studies yielded no increased risk of ovarian cancer when comparing participants exposed to talc to participants not exposed to talc (RR: 1.02; 95% CI: 0.85-1.20), I calculated that the incidence of ovarian cancer and the overall number of study participants was sufficient to detect a true risk of ovarian cancer of 1.25 with a power of .99.⁹⁰ In other words, there would be a 1% chance of being incorrect and concluding that there is no difference in risk of ovarian cancer between participants exposed and unexposed to talc if there was a true increase in risk of ovarian cancer with talc exposure.

⁸⁴ McTiernan Deposition 124.

⁸⁵ <https://seer.cancer.gov/statfacts/html/ovary.html>.

⁸⁶ Gonzalez (2016).

⁸⁷ Houghton (2014).

⁸⁸ Gates (2010); Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249.

⁸⁹ Berge 2018.

⁹⁰ Calculations performed with STATA SE 15.1, StataCorp, College Station, TX.

Dr. Moorman's power-based criticisms are similarly flawed. She relies on commentary by Narod,⁹¹ who states that "the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that despite the large size of the cohorts, the studies were not adequately powered to detect a relative risk of approximately 1.2." But this commentary rests on sample size calculations with certain assumptions regarding risk of ovarian cancer, including the same incidence rate issue that undermines Dr. McTiernan's critique. When the actual incidence rate of ovarian cancer in the cohort studies is taken into account, it decreases the study sample size needed to the sample sizes reported in the relevant cohort studies.

Relatedly, the fact that so few participants in Gonzalez (2016),⁹² Houghton (2014),⁹³ and Gates (2010)/Gertig (2000),⁹⁴ developed ovarian cancer regardless of their talc exposure does not undermine the validity of these studies. To the contrary, it demonstrates that the risk of developing ovarian cancer is small among the higher-risk populations that were studied, and that talc exposure simply does not increase that risk to a statistically significant degree.

Other plaintiffs' experts have criticized cohort studies on the grounds that they do not sufficiently account for the latency period of ovarian cancer. For example, Dr. Siemiatycki has stated that the "short follow-up periods in cohort studies would be a source of bias."⁹⁵ According to Dr. Siemiatycki, because cohort study researchers "collect information about exposure, and then follow [patients] for two years to find out how many of them got cancer, and whether there is a difference between the people who were exposed and the people who are not exposed, well, that would be pretty hopeless because it takes more than two years for cancers to develop and be diagnosed."⁹⁶ But this supposed limitation on cohort studies is greatly exaggerated. Houghton (2014) asked about talcum powder use in study participants who had been followed for up to 18 years and found no statistically significant increased risk in ovarian cancer.⁹⁷ Gates (2010) added to the Gertig (2000) cohort and followed study participants for up to 24 years and found no statistically significant elevations in risk for talc use for all epithelial ovarian cancers.⁹⁸ Similarly, Gonzalez (2016) followed participants with a sister or half-sister with a history of breast cancer for a median 6.5 years and found no association between the use of talc and ovarian cancer.⁹⁹ In any event, the women followed in all of these studies presumably did not start

⁹¹ Narod, *Talc and ovarian cancer*. (2016) 141 Gynecol. Oncol. 410. Plaintiffs' experts Drs. Ellen Blair Smith and Judith Wolf place similar reliance on Narod's commentary on the power of cohort studies to detect risk. (Blair Smith Rep. at 20; Wolf Rep. at 6.)

⁹² Gonzalez (2016).

⁹³ Houghton (2014).

⁹⁴ Gates (2010); Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249.

⁹⁵ Siemiatycki Deposition 171.

⁹⁶ *Id.*

⁹⁷ Houghton (2014).

⁹⁸ Gates (2010); Gertig (2000).

⁹⁹ Gonzalez (2016).

using talc for the first time the day the studies began and therefore would have had longer durations of use than the time period of the study – in most cases many years more.

B. Ignoring Or Minimizing The Effects Of Recall Bias And Other Biases In Case-Control Studies

Recall bias is of particular concern in retrospective case-control studies because, as compared to controls, cases “tend to search their memories to identify what might have caused their disease; healthy controls have no such motivation.”¹⁰⁰ This, in turn, tends to artificially increase the supposed effect of the exposure. As Vetter and Mascha point out, a number of factors can affect recall bias.¹⁰¹ Study participants with a particular disease tend to “search their memories to identify what might have caused their disease,” whereas “healthy controls have no such motivation.”¹⁰² Cases tend to remember past exposures more than controls, and cases are often more likely than controls to investigate whether certain risk factors increase the risk of developing a certain disease. In addition, individuals with a disease may have greater awareness of potential risk factors for their condition or may have become sensitized by repeated physician interviews. Consider again the previous example of the investigator who is trying to determine if there is a relationship between sugary drinks and high blood pressure. If the cases tend to recall and report more sugary drink consumption simply because they have reflected more on their past experiences, recall bias could result in differential misclassification and a false overestimation of the measure of risk between the sugary drinks and high blood pressure. Because cases and controls have different incentives to recall past exposures, recall bias can lead to finding associations between exposures and diseases that do not exist. As I explained earlier, the Schildkraut case-control study demonstrates an excellent example of the effect of recall bias in assessing the effects of genital talc use before and after the year 2014.

Dr. Singh attempts to minimize this finding because “there was a statistically significant increased risk both before and after 2014.”¹⁰³ This is incorrect, as there is only a statistically significant association between any genital body powder use and ovarian cancer in interviews conducted after 2014, providing an exceptional real-world example of the possibility of recall bias in a case-control epidemiologic study. Likewise, Dr. McTiernan asserts that recall bias is “unlikely” to be an issue because the studies for which data collection pre-dated news reports of this association showed similar effects to those for which data were collected afterward.¹⁰⁴ However, there is no reason to believe that recall bias did not affect cases reporting perineal talc use before 2014, since there were reports of an association in the medical literature (and presumably, the media) prior to that time – and the tendency in a case-control study for cases to remember past exposures more than controls is an issue that affects case-control studies regardless of date.

¹⁰⁰ Grimes & Schultz, *Bias and causal associations in observational research*. (2002) 259(9302) Lancet 248.

¹⁰¹ Vetter & Mascha, *Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My!*. (2017) 125(3) Anesth Analg 1042.

¹⁰² Grimes & Schultz (2002).

¹⁰³ Singh Report 45-46.

¹⁰⁴ McTiernan Report 24.

Dr. Siemiatycki also states that if recall bias were present, “we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies.”¹⁰⁵ This makes little epidemiologic sense, as recall bias is a known particular concern in retrospective studies that use a case-control design to investigate the association between exposure and outcome.¹⁰⁶

C. Jumping To Causation Without Sufficiently Determining Association

Epidemiologists and other researchers are often asked to determine whether an exposure can cause an illness. As noted above, the Bradford Hill factors supply the commonly used framework for undertaking such an analysis. But as also noted above, the existence of a clear-cut, statistically significant association is a prerequisite to such an analysis. One needs to find an association between exposure and outcome first, and it is not acceptable epidemiologic methodology to apply the Bradford Hill criteria in the absence of an established association.

Plaintiffs’ experts have the opinion that “most” or the “vast majority” of the epidemiological studies show an increased relative risk of ovarian cancer for genital talc users. For example:

- Dr. Moorman states that, “among the more than two dozen studies that have reported on the association between talc use and ovarian cancer, the vast majority of them reported relative risks or odds ratios greater than one[.]”¹⁰⁷
- Dr. Singh concludes that “[m]ost case control studies demonstrate an increased risk factor of ovarian cancer associated with talc use with an OR between 1.3 and 1.6, even after adjusting for various risk factors.”¹⁰⁸
- Dr. Smith-Bindman pronounces that her “review of case-control studies on talcum powder use and ovarian cancer risk were consistent and indicate a 50% increase in risk of serous invasive cancer related to routine talcum powder exposure compared to no exposure.”¹⁰⁹

The table in Section VII demonstrates that none of the hospital-based case-control studies, none of the cohort studies, and nearly half of the population-based case-control studies found no statistically significant association. Given that the association found in the literature is far from “perfectly clear-cut,” it is not clear to me that a Bradford Hill analysis is even appropriate in this situation.

¹⁰⁵ Siemiatycki Report 54.

¹⁰⁶ Schultz & Grimes (2002).

¹⁰⁷ Moorman Report 15.

¹⁰⁸ Singh Report 53.

¹⁰⁹ Smith-Bindman Report 34 (emphasis omitted).

D. Methodological Problems With Dr. Smith-Bindman's Meta-Analysis

One of plaintiffs' epidemiologists, Dr. Smith-Bindman, conducted her own, new meta-analysis of a portion of the talc literature for purposes of this litigation. There are significant problems with her approach that render it unreliable. The first is that the rationale for a new non-peer-reviewed meta-analysis – in an area that has already been subject to repeated meta-analyses on substantially the same body of literature – is not clearly stated. “Although this subject has hardly been studied, repeating or updating rarely (9%) leads to changes in the pooled results of meta-analyses.”¹¹⁰ Therefore, while repeated meta-analyses should not be “discouraged a priori,” an “important question” is the “rationale for repeating the analysis” and, where the results differ from prior studies, another important question is “how [the] authors defend their conclusions in relation to prior studies.”¹¹¹ Dr. Smith-Bindman does not adequately do this; nor does she subject this new meta-analysis to any form of peer review – one of the cornerstones of the body of evidence contained in the medical literature. Under a section of her report that is supposed to set forth a “rationale” for her new meta-analysis, she fails to explain the methodological shortcomings of prior meta-analyses.¹¹² Instead, she asserts that she believes that “the most important research question to answer in this review is whether regular exposure to talcum powder is associated with ovarian cancer” – and serous cancer particularly – and thus that her review should be limited to those studies that supply data for “as close to approximately daily” use of talcum powder as possible.¹¹³ But she does not explain why daily use is the right metric. Nor, in any event, does she actually limit her review to daily use, which, as she acknowledges, is not specifically examined in all of the studies she included in her review; and at the same time, she also excluded studies that did address daily use based on her own (unexplained) assessment that their “research methods were poorly defined.”¹¹⁴

Dr. Smith-Bindman reports an odds ratio of 1.43 for all ovarian cancers that is somewhat higher than prior meta-analyses,¹¹⁵ and ultimately that the association is indicative of a causal relationship.¹¹⁶ She does not explain why these results might be more valid and defensible in relation to prior meta-analyses, which report somewhat lower odds ratios and reach the opposite conclusion on causation. The sum total of her discussion on this is that “[t]he existing systematic reviews (in particular Penninkilampi and Berge) also concluded a significant increase in ovarian cancer risk following talcum powder exposure,”¹¹⁷ but she fails to acknowledge that the odds ratios were lower and that neither study embraced a causal conclusion in its review of the overall scientific literature. This omission is critical. Scientists do not practice in a vacuum; they must take into account the

¹¹⁰ Vavken & Dorotka, *A Systematic Review of Conflicting Meta-Analyses in Orthopaedic Surgery*. (2009) 467(10) Clin Orthop Relat Res. 2723.

¹¹¹ *Id.*

¹¹² Smith-Bindman Report 30.

¹¹³ *Id.* at 31.

¹¹⁴ *Id.* at 32.

¹¹⁵ *Id.* at 33.

¹¹⁶ *Id.* at 41.

¹¹⁷ *Id.* at 34.

entire existing body of scientific evidence. Dr. Smith-Bindman's failure to do so in any meaningful sense, as well as her failure to state the fact that there are no studies that investigated a standardized dose of talc, a standardized method of exposure to talc, or a validated assessment of the frequency and duration of talc usage, makes this a pointless exercise. Because of these fundamental flaws in her study, there is no valid basis to accept her unique perspective over the body of work of many other investigators over several decades that has reached the opposite conclusion.

A second problem with Dr. Smith-Bindman's approach concerns her treatment of serous ovarian cancer specifically. Dr. Smith-Bindman claims to have found data concerning serous ovarian cancer specifically from four studies.¹¹⁸ But such post-hoc analyses are often speculative because identifying subgroups after the fact can be subject to problems associated with confounding. Therefore, while these analyses may be hypothesis-generating, caution is advised in interpreting the results. For instance, if weight, socioeconomic status, race or douching each were causally related to the risk of serous ovarian cancer and also related to the use of talc but were not investigated in the post-hoc analysis because the study was not designed to look at these factors, then investigators may conclude there is an association when one does not in reality exist between talc use and serous ovarian cancer.

Identifying subgroups after the fact is also inherently prone to bias because of the investigator's impressions of the results of the study.¹¹⁹ Essentially, it allows the researcher to start with a conclusion and work backwards, which is exactly the opposite of the scientific method. And even setting aside the bias concerns in such a backwards endeavor, findings from post-hoc analyses may also be spurious because the study was not designed to address questions that are developed post-hoc, and thus, for example, no effort would have been made to match cases and controls within the subgroup.

Dr. Smith-Bindman's meta-analysis has other methodological flaws as well. For instance, Dr. Smith-Bindman stated that she alone performed "the search, according – obtaining all the papers, and then reviewing the bibliography of all those papers."¹²⁰ Most meta-analyses of higher quality involve more than one investigator to perform the search to decide what studies to include and what studies not to include in order to avoid bias. This was not done.¹²¹ She also states that Dr. Hall helped her with "abstracting the data as a second set of eyes and in doing the statistical summary."¹²² Based on her deposition, there also appear to be discrepancies between the numbers reported in Dr. Smith-Bindman's meta-analysis and those from the published literature, and she testified that she "was struggling to understand why the numbers and the figures were not exactly the same as the ones . . . in the published manuscript."¹²³ Dr. Smith-Bindman, as she stated in her

¹¹⁸ *Id.*

¹¹⁹ Wang et al., *Statistics in Medicine – Reporting of Subgroup Analyses in Clinical Trials*. (2007) 357(21) N Engl J Med 2189.

¹²⁰ Smith-Bindman Deposition (Vol. I) 101.

¹²¹ *Id.*

¹²² *Id.*

¹²³ Smith-Bindman Deposition (Vol. II) 255-56.

deposition, called Dr. Hall in between the first and second part of her deposition to ask Dr. Hall “to clarify how she did the calculations of the numbers that are shown in the figures.”¹²⁴ These irregularities further call her meta-analysis into question.

E. Methodological Errors In Plaintiffs’ Epidemiologists’ Bradford Hill Analyses

Once an association has been established, Bradford Hill set forth a framework to help assess whether a causal relationship exists: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimentation, and analogy. To the extent a Bradford Hill analysis is even called for, plaintiffs’ experts took an irregular approach that seems to be results-driven. In my discussion below, I focus on three criteria – strength of association, consistency of association and biologic gradient – that are the most relevant to my opinions and experience as an epidemiologist.

1. Plaintiffs’ epidemiologists find a “strong” association where there is none.

Strength of association measures the level of increased risk of developing a particular disease as a result of exposure to a particular substance. Strength of association is typically measured by calculating an odds ratio or relative risk – i.e., the ratio of the risk of disease in the population exposed to the risk of disease in those unexposed. A relative risk of 1.0 would indicate that there is no difference in disease risk between individuals exposed and those who are not. When the risk is low, epidemiologists typically require other strong evidence of causation.

Although there is no universal numeric definition of a “strong” association between exposure and outcome in terms of risk, it is generally accepted that ratios of risk measures between 1.1 and 2.0 represent a weak association between exposure and outcome in part because other factors (bias, confounding and random error) have the potential to explain away an apparent association of that level.¹²⁵ One after another, plaintiffs’ epidemiologists mischaracterize the – at best – weak association between talc use and ovarian cancer as one that is strong. For example:

- Dr. Siemiatycki states that “[*such*] a **high and significant** [relative risk] could not have occurred by chance.”¹²⁶
- Dr. Singh writes that he “place[s] significant weight on the fact that studies demonstrate **a strong association** between talcum powder use and ovarian cancer[.]”¹²⁷
- Dr. Moorman concludes that, “[t]aken as a whole, the **overwhelming statistical strength of these studies**, whose results are replicated over decades across a wide

¹²⁴ *Id.* 255.

¹²⁵ Wynder et al., *Radford Conference Report: Weak associations in epidemiology and their interpretation* (3rd ed.). (1982) 11 Prev. Med. 464.

¹²⁶ Siemiatycki Report 63 (emphasis added).

¹²⁷ Singh Report 63 (emphasis added).

variety of populations and investigators, further supported by consistent meta-analysis, weighs very heavily in favor of a causal inference.”¹²⁸

In his own non-peer-reviewed meta-analysis, Dr. Siemiatycki calculated the relative risk as 1.28. While I agree with Dr. Siemiatycki that a summary relative risk of 1.28, in general, represents that an exposed group has a 28% increased risk of an outcome, a relative risk in this range is weak, and may well result from bias, confounding, and/or random error rather than a true causal relationship. There is simply no disagreement about this within the scientific community. Plaintiffs’ experts’ insistence that a 1.28 relative risk is “high” raises the concern that they are pursuing a results-driven approach to their causation analysis instead of proper scientific methodology.

Furthermore, Dr. Siemiatycki states that “the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts.”¹²⁹ This might be something to consider in an ideal setting where multiple studies exist to evaluate the effect of a certain exposure that had the same design, the same conduct and the same analysis. But in this instance, in evaluating the effect of talc exposure on the risk of ovarian cancer, one cannot simply ignore the results of individual studies by lumping them together, especially when the individual studies were very different in terms of design, conduct, and analysis.

2. Plaintiffs’ experts fabricate consistency by ignoring inconsistent studies.

Plaintiffs’ experts uniformly assert that the consistency criterion has been satisfied. Dr. Singh states, for example, that “the direction and strength of association of talc and ovarian cancer is generally consistent across studies.”¹³⁰ Dr. McTiernan likewise concludes that “the association between use of talcum powder products and risk of ovarian cancer was highly consistent.”¹³¹ I would agree with plaintiffs’ experts that there are some consistencies among the studies, but those consistencies are among hospital-based case-control studies and among large cohort studies showing no statistically significant association between talc exposure and ovarian cancer. By contrast, there are inconsistencies between hospital-based and population-based case-control studies and within population-based case-control studies. As mentioned above, there are seven hospital-based case-control studies that demonstrate no statistically significant association between talc exposure and risk of ovarian cancer, while there are 26 population-based case-control studies that show inconsistent results, with some studies demonstrating a significant effect of talc exposure on risk of ovarian cancer and others showing no significant effect of talc exposure on risk of ovarian cancer. In addition, there are four cohort studies that also demonstrate no statistically significant association between talc exposure and risk of ovarian cancer. This lack of consistency both within and between study designs suggests that any association may result from bias, confounding, and/or random error, and therefore weighs against a causal relationship.

¹²⁸ Moorman Report 29 (emphasis added).

¹²⁹ Siemiatycki Report 63.

¹³⁰ Singh Report 63.

¹³¹ McTiernan Report 64.

Moreover, it is important to remember (contrary to the suggestion of several of plaintiffs' experts) that for this criterion to weigh in favor of finding a causal relationship, there must be a consistency in *statistically significant* associations. Consistency in relative risks that are not statistically significant is not meaningful because that sort of consistency does not provide any degree of confidence that the claim of association made by the study is more than random chance.

3. *Plaintiffs' experts claim there is a dose-response where none exists.*

A causal association is far more likely if there is demonstrated biological gradient – i.e., a dose-response such that a greater dose leads to a greater risk of disease incidence rate. Almost every epidemiological study has failed to show any dose-response relationship between genital talc use and ovarian cancer as described above.¹³² Indeed, plaintiffs' own expert Dr. Siemiatycki acknowledged in 2008 that “[t]he main epidemiological evidence against the association [between talc use and ovarian cancer] is the absence of clear exposure-response associations in most studies[.]”¹³³

In responding to this scientific consensus, plaintiffs' epidemiologists insist that the literature supports a finding of a dose-response relationship. For example, Dr. Siemiatycki has the opinion that “there is a clear indication of increasing risk with increasing cumulative exposure” in the Terry 2013 and Schildkraut 2016 studies.¹³⁴ But the Terry study – which Dr. Siemiatycki calls “the most important piece of evidence we have on dose-response”¹³⁵ – “observed no significant trend . . . in risk with increasing number of lifetime applications.”¹³⁶ A significant trend was found in that study only when non-users were included in the analysis. Including individuals who are not exposed to a substance in calculating a dose-response trend is inappropriate, however, because it renders this criterion redundant of the strength-of-association inquiry. Dr. Siemiatycki dismissed the fact that the p-value for the trend is not statistically significant by suggesting that “the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response.”¹³⁷ That is pure speculation; if the trend line cannot be shown to be statistically significant, then there is no way to tell whether an actual relationship exists. The Schildkraut study likewise only included findings on the difference in risk between, in essence, never-users and ever-users of talc, and its analysis is therefore not relevant to a dose-response relationship.

Indeed, determining the dose of talc exposure is problematic. As Dr. Moorman acknowledges, the relevant dose of talc is not the amount applied but the amount, if any,

¹³² Nat. Cancer Inst., *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ)* – Health Professional Version, https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#link/_220_toc (last updated Jan. 4, 2019); Gonzalez (2016); Houghton (2014); Gates (2010).

¹³³ Langseth (2008).

¹³⁴ Siemiatycki Report 63.

¹³⁵ *Id.* at 45.

¹³⁶ Terry (2013).

¹³⁷ Siemiatycki Report 44.

that actually reaches the ovaries.¹³⁸ However, there is no validated method of evaluating the amount applied, let alone how much (if any) reaches the ovaries. As previously discussed, asking a woman how much talc she powdered on to the underwear is not something that can be objectively measured. Instead, it is inherently subjective and prone to inaccurate estimation. As also discussed above, this creates the potential for recall, reporting, and measurement bias, all of which can lead to false conclusions based on the results. For all of these reasons, the potential for inaccurate classification of exposure leads to tremendous limitations in the entire body of relevant literature, limiting the ability to conclude that there is a causal relationship between talc exposure and ovarian cancer.

IX. SUMMARY AND CONCLUSIONS ASSESSING CAUSALITY

In designing an epidemiological study, the goal of a scientist is to derive findings that represent the truth in the population being studied. In this respect, choosing a study design that minimizes or eliminates the effects of bias and confounding is very important. In the context of assessing whether epidemiological studies indicate an association between genital talc use and ovarian cancer, recall bias is of particular concern among case-control studies and has demonstrably affected findings of association.

The methodologies used by plaintiffs' experts ignore fundamental principles of epidemiology. In particular, plaintiffs' experts ignore the hierarchy of evidence in evaluating studies and rely on study designs that are inherently susceptible to bias. Specifically, plaintiffs' experts pay particular attention to criticizing cohort studies, with little acknowledgment of the limitations in the case-control studies that find weak associations.

Plaintiffs' experts generally agree that even the studies that do show an association between talc use and ovarian cancer have found a relative risk in the range of 1.2-1.6. This, by definition, is a weak association. Plaintiffs' epidemiologists nonetheless characterize the association as "strong." Likewise, plaintiffs' epidemiologists try to demonstrate a dose-response relationship by relying on methodologically flawed studies and statistically insignificant trend lines. They also see consistency where the studies are inherently inconsistent.

As a professor of medicine and of public health, I have focused my career on using the science of epidemiology as a scientific tool to help improve our understanding of health and disease. The distortion of epidemiological science for purposes of litigation does not achieve those goals. Instead, it undermines scientific efforts to better understand the etiology of disease.

When analyzed in a methodological manner, the body of medical literature simply does not support the conclusion that perineal exposure to talc causes ovarian cancer.

¹³⁸

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APPENDIX A

Curriculum Vitae for Academic Promotion
The Johns Hopkins University School of Medicine



Christian A. Merlo, M.D., M.P.H.

February 22, 2019

DEMOGRAPHIC AND PERSONAL INFORMATION

Current Appointments

2006-2015	Assistant Professor of Medicine, Johns Hopkins University School of Medicine
2009-2015	Assistant Professor of Epidemiology, Johns Hopkins University Bloomberg School of Public Health
2010-present	Associate Program Director for Scholarship, Osler House Staff Program, Johns Hopkins University School of Medicine
2014-present	Director of Outpatient Services, Johns Hopkins Division of Pulmonary and Critical Care Medicine
2015-present	Associate Program Director, Adult Cystic Fibrosis Center, Johns Hopkins Cystic Fibrosis Center
2015-present	Associate Professor of Medicine, Johns Hopkins University School of Medicine
2015-present	Associate Professor of Epidemiology, Johns Hopkins University Bloomberg School of Public Health

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Education and Training

Undergraduate

1992 A.B., Biology/Visual Arts, The College of The Holy Cross, Worcester, MA, *cum laude*

Doctoral/graduate

1996 M.D., Georgetown University School of Medicine, Washington, DC

2003 M.P.H., Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

Postdoctoral

1996-1997	Intern, Internal Medicine, Georgetown University School of Medicine, Washington, DC
1997-1999	Resident, Internal Medicine, Georgetown University School of Medicine, Washington, DC
1999-2000	Chief Resident, Internal Medicine, Georgetown University School of Medicine, Washington, DC
2000-2001	Clinical Fellow, Division of Pulmonary & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
2001-2004	Research Fellow, Division of Pulmonary & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Professional Experience:

1999-2000 Instructor, Georgetown University School of Medicine, Washington, DC

2003-2004	Intensivist, Virginia Hospital Center, Arlington, VA
2004-2006	Instructor, Johns Hopkins University School of Medicine, Baltimore, MD
2006-2015	Assistant Professor, Johns Hopkins University School of Medicine, Baltimore, MD
2009-2015	Assistant Professor of Epidemiology, Department of Epidemiology, JHSPH
2015-present	Associate Professor, Johns Hopkins University School of Medicine, Baltimore, MD
2015-present	Associate Professor of Epidemiology, Department of Epidemiology, JHSPH

RESEARCH ACTIVITIES

Peer Reviewed Original Science Publications

1. Lechtzin N, John M, Irizarry R, **Merlo C**, Diette GB, Boyle MP. Outcomes of adults with cystic fibrosis infected with antibiotic-resistant *Pseudomonas aeruginosa*. *Respiration* 2006; 73: 27-33.
2. Wright JM, **Merlo CA**, Reynolds JB, Zeitlin PL, Garcia JG, Guggino WB, Boyle MP. Respiratory epithelial gene expression in patients with mild and severe cystic fibrosis lung disease. *Am J Respir Cell Mol Biol* 2006; 35: 327-336.
3. Buranawuti K, Boyle MP, Cheng S, Steiner LL, McDougal K, Fallin MD, **Merlo C**, Zeitlin PL, Rosenstein BJ, Mogayzel PJ Jr, Wang X, Cutting GR. Variants in mannose-binding lectin and tumour necrosis factor alpha affect survival in cystic fibrosis. *J Med Genet* 2007; 44: 209-214.
4. Hsu SC, Groman JD, **Merlo CA**, Naughton K, Zeitlin PL, Germain-Lee EL, Boyle MP, Cutting GR. Patients with mutations in Gsalpha have reduced activation of a downstream target in epithelial tissues due to haploinsufficiency. *J Clin Endocrinol Metab* 2007; 92: 3941-3948.
5. Kirk GD, **Merlo C**, O'Driscoll P, Mehta SH, Galai N, Vlahov D, Samet J, Engels EA. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007; 45: 103-110.
6. **Merlo CA**, Boyle MP, Diener-West M, Marshall BC, Goss CH, Lechtzin N. Incidence and risk factors for multiple antibiotic-resistant *Pseudomonas aeruginosa* in cystic fibrosis. *Chest* 2007; 132: 562-568.
7. Dasenbrook EC, **Merlo CA**, Diener-West M, Lechtzin N, Boyle MP. Persistent methicillin-resistant *Staphylococcus aureus* and rate of FEV1 decline in cystic fibrosis. *Am J Respir Crit Care Med* 2008; 178: 814-821.
8. Allen JG, Weiss ES, **Merlo CA**, Baumgartner WA, Conte JV, Shah AS. Impact of donor-recipient race matching on survival after lung transplantation: analysis of over 11,000 patients. *J Heart Lung Transplant* 2009; 28: 1063-1071.
9. **Merlo CA**, Weiss ES, Orens JB, Borja MC, Diener-West M, Conte JV, Shah AS. Impact of U.S. Lung Allocation Score on survival after lung transplantation. *J Heart Lung Transplant* 2009; 28: 769-775.
10. Weiss ES, Allen JG, Meguid RA, Patel ND, **Merlo CA**, Orens JB, Baumgartner WA, Conte JV, Shah AS. The impact of center volume on survival in lung transplantation: an analysis of more than 10,000 cases. *Ann Thorac Surg* 2009; 88: 1062-1070.
11. Weiss ES, Allen JG, **Merlo CA**, Conte JV, Shah AS. Lung allocation score predicts survival in lung transplantation patients with pulmonary fibrosis. *Ann Thorac Surg* 2009; 88: 1757-1764.
12. Weiss ES, Allen JG, **Merlo CA**, Conte JV, Shah AS. Survival after single versus bilateral lung transplantation for high-risk patients with pulmonary fibrosis. *Ann Thorac Surg* 2009; 88: 1616-25; discussion 1625-6.
13. Weiss ES, Allen JG, Modi MN, **Merlo CA**, Conte JV, Shah AS. Lung transplantation in older patients with cystic fibrosis: analysis of UNOS data. *J Heart Lung Transplant* 2009; 28: 135-140.
14. Weiss ES, **Merlo CA**, Shah AS. Impact of advanced age in lung transplantation: an analysis of United Network for Organ Sharing data. *J Am Coll Surg* 2009; 208: 400-409.
15. Allen JG, Arnaoutakis GJ, Weiss ES, **Merlo CA**, Conte JV, Shah AS. The impact of recipient body mass index on survival after lung transplantation. *J Heart Lung Transplant* 2010; 29: 1026-1033.
16. Arnaoutakis GJ, Allen JG, **Merlo CA**, Baumgartner WA, Conte JV, Shah AS. Low potassium dextran is superior to University of Wisconsin solution in high-risk lung transplant recipients. *J Heart Lung Transplant* 2010; 29: 1380-1387.
17. Dasenbrook EC, Checkley W, **Merlo CA**, Konstan MW, Lechtzin N, Boyle MP. Association between respiratory tract methicillin-resistant *Staphylococcus aureus* and survival in cystic fibrosis. *JAMA* 2010; 303: 2386-2392.
18. Drummond MB, Kirk GD, McCormack MC, Marshall MM, Ricketts EP, Mehta SH, Wise RA, **Merlo CA**. HIV and COPD: impact of risk behaviors and diseases on quality of life. *Qual Life Res* 2010; 19: 1295-1302.
19. Drummond MB, Kirk GD, Ricketts EP, McCormack MC, Hague JC, McDyer JF, Mehta SH, Engels EA, Wise RA, **Merlo CA**. Cross sectional analysis of respiratory symptoms in an injection drug user cohort: the impact of obstructive lung disease and HIV. *BMC Pulm Med* 2010; 10: 27-2466-10-27.
20. Hoag JB, Terry P, Mitchell S, Reh D, **Merlo CA**. An epistaxis severity score for hereditary hemorrhagic

- telangiectasia. *Laryngoscope* 2010; 120: 838-843.
21. Weiss ES, Allen JG, **Merlo CA**, Conte JV, Shah AS. Factors indicative of long-term survival after lung transplantation: a review of 836 10-year survivors. *J Heart Lung Transplant* 2010; 29: 240-246.
22. Allen JG, Arnaoutakis GJ, Orens JB, McDyer J, Conte JV, Shah AS, **Merlo CA**. Insurance status is an independent predictor of long-term survival after lung transplantation in the United States. *J Heart Lung Transplant* 2011; 30: 45-53.
23. Arnaoutakis GJ, Allen JG, **Merlo CA**, Sullivan BE, Baumgartner WA, Conte JV, Shah AS. Impact of the lung allocation score on resource utilization after lung transplantation in the United States. *J Heart Lung Transplant* 2011; 30: 14-21.
24. Arnaoutakis GJ, George TJ, Alejo DE, **Merlo CA**, Baumgartner WA, Cameron DE, Shah AS. Society of Thoracic Surgeons Risk Score predicts hospital charges and resource use after aortic valve replacement. *J Thorac Cardiovasc Surg* 2011; 142: 650-655.
25. Arnaoutakis GJ, George TJ, Robinson CW, Gibbs KW, Orens JB, **Merlo CA**, Shah AS. Severe acute kidney injury according to the RIFLE (risk, injury, failure, loss, end stage) criteria affects mortality in lung transplantation. *J Heart Lung Transplant* 2011; 30: 1161-1168.
26. Drummond MB, Kirk GD, Astemborski J, McCormack MC, Marshall MM, Mehta SH, Wise RA, **Merlo CA**. Prevalence and risk factors for unrecognized obstructive lung disease among urban drug users. *Int J Chron Obstruct Pulmon Dis* 2011; 6: 89-95.
27. George TJ, Arnaoutakis GJ, **Merlo CA**, Kemp CD, Baumgartner WA, Conte JV, Shah AS. Association of operative time of day with outcomes after thoracic organ transplant. *JAMA* 2011; 305: 2193-2199.
28. Marshall MM, Kirk GD, Caporaso NE, McCormack MC, **Merlo CA**, Hague JC, Mehta SH, Engels EA. Tobacco use and nicotine dependence among HIV-infected and uninfected injection drug users. *Addict Behav* 2011; 36: 61- 67.
29. Sheridan MB, Hefferon TW, Wang N, **Merlo C**, Milla C, Borowitz D, Green ED, Mogayzel PJ Jr, Cutting GR. CFTR transcription defects in pancreatic sufficient cystic fibrosis patients with only one mutation in the coding region of CFTR. *J Med Genet* 2011; 48: 235-241.
30. Tam V, Arnaoutakis GJ, George TJ, Russell SD, **Merlo CA**, Conte JV, Baumgartner WA, Shah AS. Marital status improves survival after orthotopic heart transplantation. *J Heart Lung Transplant* 2011; 30: 1389-1394.
31. West NE, Lechtzin N, **Merlo CA**, Turowski JB, Davis ME, Ramsay MZ, Watts SL, Stenner SP, Boyle MP. Appropriate goal level for 25-hydroxyvitamin D in cystic fibrosis. *Chest* 2011; 140: 469-474.
32. Drummond MB, Kirk GD, Astemborski J, Marshall MM, Mehta SH, McDyer JF, Brown RH, Wise RA, **Merlo CA**. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax* 2012; 67: 309-314.
33. Eberlein M, Arnaoutakis GJ, Yarmus L, Feller-Kopman D, Dezube R, Chahla MF, Bolukbas S, Reed RM, Klesney-Tait J, Parekh KR, **Merlo CA**, Shah AS, Orens JB, Brower RG. The effect of lung size mismatch on complications and resource utilization after bilateral lung transplantation. *J Heart Lung Transplant* 2012; 31: 492-500.
34. George TJ, Arnaoutakis GJ, Beaty CA, Pipeling MR, **Merlo CA**, Conte JV, Shah AS. Acute kidney injury increases mortality after lung transplantation. *Ann Thorac Surg* 2012; 94: 185-192.
35. George TJ, Beaty CA, Kilic A, Shah PD, **Merlo CA**, Shah AS. Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. *J Heart Lung Transplant* 2012; 31: 1182-1191.
36. Kilic A, George TJ, Beaty CA, **Merlo CA**, Conte JV, Shah AS. The effect of center volume on the incidence of postoperative complications and their impact on survival after lung transplantation. *J Thorac Cardiovasc Surg* 2012; 144: 1502-8; discussion 1508-9.
37. Kilic A, **Merlo CA**, Conte JV, Shah AS. Lung transplantation in patients 70 years old or older: have outcomes changed after implementation of the lung allocation score? *J Thorac Cardiovasc Surg* 2012; 144: 1133-1138.
38. Drummond MB, **Merlo CA**, Astemborski J, Kalmin MM, Kisalu A, McDyer JF, Mehta SH, Brown RH, Wise RA, Kirk GD. The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. *AIDS* 2013; 27: 1303-1311.
39. Eberlein M, Diehl E, Bolukbas S, **Merlo CA**, Reed RM. An oversized allograft is associated with improved survival after lung transplantation for idiopathic pulmonary arterial hypertension. *J Heart Lung Transplant* 2013; 32: 1172-1178.
40. Eberlein M, Reed RM, Bolukbas S, Parekh KR, Arnaoutakis GJ, Orens JB, Brower RG, Shah AS, Hunsicker L, **Merlo CA**. Lung size mismatch and survival after single and bilateral lung transplantation. *Ann Thorac Surg* 2013; 96: 457-463.
41. Eberlein M, Reed RM, Madaa M, Bolukbas S, Arnaoutakis GJ, Orens JB, Brower RG, **Merlo CA**, Hunsicker LG.

- Donor-recipient size matching and survival after lung transplantation. A cohort study. *Ann Am Thorac Soc* 2013; 10: 418-425.
42. Kilic A, Beaty CA, **Merlo CA**, Conte JV, Shah AS. Functional status is highly predictive of outcomes after redo lung transplantation: an analysis of 390 cases in the modern era. *Ann Thorac Surg* 2013; 96: 1804-11; discussion 1811.
43. Kilic A, Shah AS, **Merlo CA**, Gourin CG, Lidor AO. Early outcomes of antireflux surgery for United States lung transplant recipients. *Surg Endosc* 2013; 27: 1754-1760.
44. Reh DD, Hur K, **Merlo CA**. Efficacy of a topical sesame/rose geranium oil compound in patients with hereditary hemorrhagic telangiectasia associated epistaxis. *Laryngoscope* 2013; 123: 820-822.
45. Yarmus L, Akulian J, Gilbert C, Illei P, Shah P, **Merlo C**, Orens J, Feller-Kopman D. Cryoprobe transbronchial lung biopsy in patients after lung transplantation: a pilot safety study. *Chest* 2013; 143: 621-626.
46. Drummond MB, Astemborski J, Lambert AA, Goldberg S, Stitzer ML, **Merlo CA**, Rand CS, Wise RA, Kirk GD. A randomized study of contingency management and spirometric lung age for motivating smoking cessation among injection drug users. *BMC Public Health* 2014; 14: 761-2458-14-761.
47. Fischer WA, Drummond MB, **Merlo CA**, Thomas DL, Brown R, Mehta SH, Wise RA, Kirk GD. Hepatitis C virus infection is not an independent risk factor for obstructive lung disease. *COPD* 2014; 11: 10-16.
48. Gashouta MA, **Merlo CA**, Pipeling MR, McDyer JF, Hayanga JW, Orens JB, Girgis RE. Serial monitoring of exhaled nitric oxide in lung transplant recipients. *J Heart Lung Transplant* 2014.
49. Hulbert A, Hooker CM, Keruly JC, Brown T, Horton K, Fishman E, Rodgers K, Lee B, Sam C, Tsai S, Weihe E, Pridham G, Drummond B, **Merlo C**, Geronimo M, Porter M, Cox S, Li D, Harline M, Teran M, Wrangle J, Mudge B, Taylor G, Kirk GD, Herman JG, Moore RD, Brown RH, Brock MV. Prospective CT screening for lung cancer in a high-risk population: HIV-positive smokers. *J Thorac Oncol* 2014; 9: 752-759.
50. Kilic A, Conte JV, Baumgartner WA, Russell SD, **Merlo CA**, Shah AS. Does recipient age impact functional outcomes of orthotopic heart transplantation? *Ann Thorac Surg* 2014; 97: 1636-1642.
51. **Merlo CA**, Yin LX, Hoag JB, Mitchell SE, Reh DD. The effects of epistaxis on health-related quality of life in patients with hereditary hemorrhagic telangiectasia. *Int Forum Allergy Rhinol* 2014; 4: 921-925.
52. Popescu I, Drummond MB, Gama L, Coon T, **Merlo CA**, Wise RA, Clements JE, Kirk GD, McDyer JF. Activation- induced cell death drives profound lung CD4(+) T-cell depletion in HIV-associated chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014; 190: 744-755.
53. Reh DD, Yin LX, Laaeq K, **Merlo CA**. A new endoscopic staging system for hereditary hemorrhagic telangiectasia. *Int Forum Allergy Rhinol* 2014; 4: 635-639.
54. Grimm JC, Valero V 3rd, Kilic A, Crawford TC, Conte JV, **Merlo CA**, Shah PD, Shah AS. Preoperative performance status impacts perioperative morbidity and mortality after lung transplantation. *Ann Thorac Surg* 2015; 99: 482-489.
55. **Merlo CA**, Clark SC, Arnaoutakis GJ, Yonan N, Thomas D, Simon A, Thompson R, Thomas H, Orens JB, Shah AS. National health care delivery systems influence lung transplant outcomes for cystic fibrosis. *American Journal of Transplantation* 2015; Epub March 24.
56. Braun AT, Dasenbrook EC, Shah AS, Orens JB, **Merlo CA**. Impact of lung allocation score on survival in cystic fibrosis lung transplant recipients. *J Heart Lung Transplant*. 2015; Epub Jun 11.
57. Grimm JC, Valero V 3rd, Kilic A, Magruder JT, **Merlo CA**, Shah PD, Shah AS. Association Between Prolonged Graft Ischemia and Primary Graft Failure or Survival Following Lung Transplantation. *JAMA Surg*. 2015 Jun;150(6):547-53. doi: 10.1001/jamasurg.2015.12. PubMed PMID: 25874575.
58. Yin LX, Reh DD, Hoag JB, Mitchell SE, Mathai SC, Robinson GM, **Merlo CA**. The minimal important difference of the epistaxis severity score in hereditary hemorrhagic telangiectasia. *Laryngoscope*. 2015; Epub Sep 22.
59. Grimm JC, Valero V 3rd, Magruder JT, Kilic A, Dungan SP, Silhan LL, Shah PD, Kim BS, **Merlo CA**, Sciortino CM, Shah AS. A novel risk score that incorporates recipient and donor variables to predict 1-year mortality in the current era of lung transplantation. *J Heart Lung Transplant*. 2015 Nov;34(11):1449-54. doi: 10.1016/j.healun.2015.07.001. Epub 2015 Jul 22. PubMed PMID: 26275639.
60. Walker-Sperling VE, **Merlo CA**, Buckheit RW 3rd, Lambert A, Tarwater P, Kirk GD, Drummond MB, Blankson JN. HIV Controller T Cells Effectively Inhibit Viral Replication in Alveolar Macrophages. *AIDS Res Hum Retroviruses*. 2016 Aug 2. [Epub ahead of print] PubMed PMID: 27353255.
61. Mock JR, Kolb TM, Illei PB, Yang SC, Lederman HM, **Merlo CA**. Bronchus-associated Lymphoid Tissue in Kabuki Syndrome with Associated Hyper-IgM Syndrome/Common Variable Immunodeficiency. *Am J Respir Crit Care Med*. 2016 Aug 15;194(4):514-5. doi: 10.1164/rccm.201511-2305IM. PubMed PMID: 27275756.
62. Popescu I, Drummond MB, Gama L, Lambert A, Hoji A, Coon T, **Merlo CA**, Wise RA, Keruly J, Clements JE,

- Kirk GD, McDyer JF. HIV Suppression Restores the Lung Mucosal CD4+ T-Cell Viral Immune Response and Resolves CD8+ T-Cell Alveolitis in Patients at Risk for HIV-Associated Chronic Obstructive Pulmonary Disease. *J Infect Dis.* 2016 Nov 15;214(10):1520-1530. Epub 2016 Sep 9. PubMed PMID: 27613775; PubMed Central PMCID: PMC5091376.
63. Walker-Sperling VE, **Merlo CA**, Buckheit RW 3rd, Lambert A, Tarwater P, Kirk GD, Drummond MB, Blankson JN. Short Communication: HIV Controller T Cells Effectively Inhibit Viral Replication in Alveolar Macrophages. *AIDS Res Hum Retroviruses.* 2016 Oct/Nov;32(10-11):1097-1099. Epub 2016 Aug 2. PubMed PMID: 27353255; PubMed Central PMCID: PMC5067835.
64. Whitehead KJ, Sautter NB, McWilliams JP, Chakinala MM, **Merlo CA**, Johnson MH, James M, Everett EM, Clancy MS, Faughnan ME, Oh SP, Olitsky SE, Pyritz RE, Gossage JR. Effect of Topical Intranasal Therapy on Epistaxis Frequency in Patients With Hereditary Hemorrhagic Telangiectasia: A Randomized Clinical Trial. *JAMA.* 2016 Sep 6;316(9):943-51. doi: 10.1001/jama.2016.11724. PubMed PMID: 27599329.
65. Magruder JT, Crawford TC, Grimm JC, Kim B, Shah AS, Bush EL, Higgins RS, **Merlo CA**. Risk Factors for De Novo Malignancy Following Lung Transplantation. *Am J Transplant.* 2017 Jan;17(1):227-238. doi: 10.1111/ajt.13925. Epub 2016 Aug 25. PubMed PMID: 27321167.
66. Magruder JT, Shah AS, Crawford TC, Grimm JC, Kim B, Orens JB, Bush EL, Higgins RS, **Merlo CA**. Simulated Regionalization of Heart and Lung Transplantation in the United States. *Am J Transplant.* 2017 Feb;17(2):485-495. doi: 10.1111/ajt.13967. Epub 2016 Sep 12. PubMed PMID: 27618731.
67. Drummond MB, Lambert AA, Hussien AF, Lin CT, **Merlo CA**, Wise RA, Kirk GD, Brown RH. HIV Infection Is Independently Associated with Increased CT Scan Lung Density. *Acad Radiol.* 2017 Feb;24(2):137-145. doi: 10.1016/j.acra.2016.09.019. Epub 2016 Nov 18. PubMed PMID: 27876271; PubMed Central PMCID: PMC5237394.
68. Jennings MT, Dezube R, Paranjape S, West NE, Hong G, Braun A, Grant J, **Merlo CA**, Lechtzin N. An Observational Study of Outcomes and Tolerances in Patients with Cystic Fibrosis Initiated on Lumacaftor/Ivacaftor. *Ann Am Thorac Soc.* 2017 Apr 13. doi: 10.1513/AnnalsATS.201701-058OC. [Epub ahead of print] PubMed PMID: 28406713.
69. Jennings MT, Dasenbrook EC, Lechtzin N, Boyle MP, **Merlo CA**. Risk factors for persistent methicillin-resistant *Staphylococcus aureus* infection in cystic fibrosis. *J Cyst Fibros.* 2017 Apr 23. pii: S1569-1993(17)30106-6. doi: 10.1016/j.jcf.2017.04.010. [Epub ahead of print] PubMed PMID: 28446387.
70. Crawford TC, Grimm JC, Magruder JT, Ha J, Sciortino CM, Kim BS, Bush EL, Conte JV, Higgins RS, Shah AS, **Merlo CA**. Lung Transplant Mortality Is Improving in Recipients With a Lung Allocation Score in the Upper Quartile. *Ann Thorac Surg.* 2017 May;103(5):1607-1613. doi: 10.1016/j.athoracsur.2016.11.057. Epub 2017 Feb 21. PubMed PMID: 28223052.
71. Crawford TC, Magruder JT, Grimm JC, Suarez-Pierre A, Zhou X, Ha JS, Higgins RS, Broderick SR, Orens JB, Shah P, **Merlo CA**, Kim BS, Bush EL. Impaired Renal Function Should Not Be a Barrier to Transplantation in Patients With Cystic Fibrosis. *Ann Thorac Surg.* 2017 Aug 16. pii: S0003-4975(17)30707-5. doi: 10.1016/j.athoracsur.2017.05.032. [Epub ahead of print] PubMed PMID: 28822537.
72. Reed RM, Cabral HJ, Dransfield MT, Eberlein M, Merlo CA, Mulligan MJ, Netzer G, Sanchez PG, Scharf SM, Sin DD, Celli BR. Survival of Lung Transplant Candidates With COPD: BODE Score Reconsidered. *Chest.* 2018 Mar;153(3):697-701.
73. Orens JB, Merlo CA. Selection of Candidates for Lung Transplantation and Controversial Issues. *Semin Respir Crit Care Med.* 2018 Apr;39(2):117-125.
74. Crawford TC, Lui C, Magruder JT, Ha JS, Higgins RS, Merlo CA, Kim BS, Bush EL. Five-year mortality hazard is reduced in chronic obstructive pulmonary disease patients receiving double- versus single-lung transplants. *J Surg Res.* 2018 Jun 2.
75. Hong G, Psoter KJ, Jennings MT, Merlo CA, Boyle MP, Hadjiliadis D, Kawut SM, Lechtzin N. Risk factors for persistent *Aspergillus* respiratory isolation in cystic fibrosis. *J Cyst Fibros.* 2018 Sep;17(5):624-630.
76. Crawford TC, Lui C, Magruder JT, Suarez-Pierre A, Ha JS, Higgins RS, Broderick SR, Merlo CA, Kim BS, Bush EL. Traumatically Brain-Injured Donors and the Impact on Lung Transplantation Survival. *Ann Thorac Surg.* 2018 Sep;106(3):842-847.
77. Hsu J, Krishnan A, Lin CT, Shah PD, Broderick SR, Higgins RSD, Merlo CA, Bush EL. Sarcopenia of the Psoas Muscles is Associated with Poor Outcomes Following Lung Transplantation. *Ann Thorac Surg.* 2018 Nov 14;.
78. Sharma N, Evans TA, Pellicore MJ, Davis E, Aksit MA, McCague AF, Joynt AT, Lu Z, Han ST, Anzmann AF, Lam AN, Thaxton A, West N, Merlo C, Gottschalk LB, Raraigh KS, Sosnay PR, Cotton CU, Cutting GR. Capitalizing on the heterogeneous effects of CFTR nonsense and frameshift variants to inform therapeutic strategy for cystic fibrosis. *PLoS Genet.* 2018 Nov;14(11):e1007723.

79. Fraser CD 3rd, Zhou X, Grimm JC, Suarez-Pierre A, Crawford TC, Lui C, Bush EL, Hibino N, Jacobs ML, Vricella LA, Merlo C. Size Mismatching Increases Mortality Following Lung Transplantation in Pre-Adolescent Patients. *Ann Thorac Surg*. 2019 Feb 11;.

Invited Reviews

1. **Merlo CA**, Boyle MP. Modifier genes in cystic fibrosis lung disease. *J Lab Clin Med* 2003;141:237-41.
2. **Merlo CA**, Orens JB. Candidate selection, overall results, and choosing the right operation. *Semin Respir Crit Care Med* 2010;31:99-107.
3. Braun AT, **Merlo CA**. Cystic fibrosis lung transplantation. *Curr Opin Pulm Med* 2011;17:467-72.
4. Kirk GD, **Merlo CA**, For the Lung HIV Study Group. HIV infection in the etiology of lung cancer: confounding, causality, and consequences. *Proc Am Thorac Soc* 2011;8:326-32.
5. Lambert AA, **Merlo CA**, Kirk GD. Human immunodeficiency virus-associated lung malignancies. *Clin Chest Med* 2013;34:255-72.

Inventions, Patents, Copyrights

- 2010 **Merlo CA**, Reh DR, Hoag JB. Method and severity scale for measuring epistaxis among patients with hereditary hemorrhagic telangiectasia (HHT). Used worldwide as a primary outcome in HHT interventional clinical trials.

Extramural Sponsorship (current, pending, previous)

Current Grants

- | | |
|---------------------|---|
| 09/26/13 – 07/31/18 | <u>Immune Mechanisms of HIV-associated COPD</u>
U01HL121814
NIH
\$505,539
PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)
Role: Co-I
0.60 calendar months
This proposal directly addresses critical gaps in our understanding of the clinical spectrum and consequences of HIV-associated COPD and will identify key biologic mechanisms contributing to the disease. Findings will inform the clinical management and development of interventions targeting HIV associated COPD, and may also inform broader strategies for COPD in non-HIV infected populations. |
| 07/01/14 – 06/30/19 | <u>Clinical Risk Factors for Primary Graft Dysfunction</u>
R01HL087115
NIH subaward
\$19,984
PI: Jason Christie, MD (University of Pennsylvania)
Role: Co-I
0.12 calendar months
The major goal of this multicenter study is to define risk factors for the development of primary graft dysfunction following lung transplantation. |
| 09/01/14 – 08/31/18 | <u>Predictors, consequences and mechanisms of accelerated lung aging in HIV</u>
R01HL126549
NIH
\$499,997
PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)
Role: Co-I
0.60 calendar months
The goal of this program is to establish risk factors, associated co-morbidities, and immunologic and inflammatory biomarkers associated with accelerated decline in lung function in the SHIELD cohort of HIV-positive inner-city intravenous drug users. |
| 07/01/15 – 06/30/18 | <u>Transition of Care for Patients with Cystic Fibrosis who Undergo Lung Transplantation</u>
Spruance Foundation II Discovery Fund |

\$300,000

PI: Christian Merlo, MD MPH

2.4 calendar months

The major goal of this proposal is to identify factors which may help to improve the process of lung transplantation for patients with cystic fibrosis.

Previous

07/01/03 – 06/30/04

Gene Expression Analysis of Nasal Respiratory Epithelial Cells in Δ F508/ Δ F508 Individuals with Mild and Severe Cystic Fibrosis Lung Disease

Bauernschmidt Fellowship in Pulmonary Disease

Eudowood Foundation

\$35000

Role: PI

The goal of this study was to evaluate differences in gene expression between patients with cystic fibrosis with mild and severe lung disease.

07/01/04 – 06/30/07

The Effect of Multiple Antibiotic Resistant *Pseudomonas aeruginosa* on Outcomes in Cystic Fibrosis

The Harry Shwachman Clinical Investigator Award

Cystic Fibrosis Foundation

\$270000

Role: PI

6.0 calendar months

The goal of this study was to evaluate the impact of multiple antibiotic resistant *Pseudomonas aeruginosa* (MARPA) on outcomes among patients with cystic fibrosis.

07/01/06 – 06/30/07

Emphysema and HIV infection within the ALIVE cohort in Baltimore

Thomas and Carol McCann Innovative research Fund for Asthma and Respiratory Disease

\$35000

Role: Co-PI

The main goal of this study was to evaluate the association between emphysema and HIV infection among the ALIVE cohort in Baltimore.

01/01/08 – 12/30/12

The Study of HIV Infection in the Etiology of Lung Disease (SHIELD)

RFAHL07008

NIH

\$549,598

PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)

Role: Co-PI

0.60 calendar months

06/01/11 – 02/28/15

North American Study of Epistaxis in HHT (NOSE)

Hereditary Hemorrhagic Telangiectasia Foundation

\$11,126

Role: site PI

0.12 calendar months

This was a multicenter randomized placebo-controlled trial comparing bevacizumab, estrogen, tranexamic acid, and placebo in patients with HHT-related epistaxis.

09/06/12 – 06/30/14

Using mHealth to Respond Early to Acute Exacerbations of COPD in HIV mREACH

R34HL117349

NIH

\$376,291

PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)

Role: Co-I

0.60 calendar months

This clinical trial planning grant evaluated the feasibility, acceptability and defined optimal trial elements for an m-Health intervention to identify early exacerbations in HIV-COPD to improve management and clinical outcomes.

Research Program Building / Leadership:

- 2010-present Associate Program Director for Scholarship, Osler Residency Program, Johns Hopkins University School of Medicine. In my capacity, I am responsible for the research experience for the Osler House Staff throughout residency training. This involves one on one meetings to discuss research interests and goals, an online lecture series providing an introduction to research, pairing with faculty mentors, mentorship in the presentation of research projects at local and national meetings, collecting data highlighting scholarly activity, and reporting these data to the Director for internal use as well as for ACGME purposes.
- 2010-present Director of Research, The Johns Hopkins Lung Transplant Program. In my capacity, I am responsible for coordination of research efforts within the lung transplant program. This involves multidisciplinary projects spanning across many disciplines (Medicine, Surgery, Rehabilitation, Psychology, Epidemiology) as well as across different levels of training from faculty, fellows, residents, and medical students.
- 2010-2018 Director, Hereditary Hemorrhagic Telangiectasia Center of Excellence. In my capacity, I am responsible for the coordination of multicenter clinical trials as well as local investigations among patients with HHT. Our center was responsible for creation of an epistaxis severity score (HHT-ESS), the first objective measure of epistaxis severity, now used worldwide clinically as well as an outcome measure in HHT clinical investigations.
- 2016-present Associate Director, The Johns Hopkins Adult Cystic Fibrosis Program. In my capacity, I am responsible for the coordination of aspects of clinical and research coordination for our cystic fibrosis program.
- 2016-present Director of Research, The Johns Hopkins Adult Cystic Fibrosis Program. In my capacity, I am responsible for coordination of research efforts within the Adult CF program. This involves multidisciplinary projects spanning across many disciplines (Medicine, Surgery, Psychology, Epidemiology) as well as across different levels of training from faculty, fellows, residents, and medical students.

EDUCATIONAL ACTIVITIES

Educational Publications

Peer-reviewed, original, educational publications – None

Review Articles – None

Editorials – None

Case Reports

1. **Merlo CA**, Studer SM, Conte JV, Yang SC, Sonnett J, Orens JB. The course of neurofibromatosis type 1 on immunosuppression after lung transplantation: report of 2 cases. J Heart Lung Transplant 2004; 23: 774-776.
2. Houston B, Reiss KA, **Merlo C**. Healthy, but comatose. Am J Med 2011; 124: 303-305.

Book and Book Chapters

1. **Merlo CA**, Boyle MP. "Adult Cystic Fibrosis". In The Osler Medical Handbook. Mosby. Philadelphia: 60, 899-911, 2003.
2. **Merlo CA**, Terry PB. Concise Review: Diagnosis and management of pulmonary arteriovenous malformations. In Harrison's Online. 2002. <http://www.harrisonsonline.com>.
3. **Merlo CA**, Hansel N. "Have a working knowledge of EMTALA laws as they apply to the ICU. How to be a good referring and accepting ICU physician". In Avoiding Common ICU Errors. Lippincott. 2008.
4. **Merlo CA**. Critical Care Medicine. In First Aid for the Internal Medicine Boards. McGraw-Hill. New York: 16, 123-132, 2010.

5. **Merlo CA.** Pulmonary Medicine. In First Aid for the Internal Medicine Boards. McGraw-Hill. New York: 4, 553-580, 2010.
6. Dasenbrook EC, **Merlo CA.** "Cystic Fibrosis and Bronchiectasis". In Lung Transplantation. Informa. 2010.
7. Hayes M, **Merlo CA.** "Hemoptysis". The Principles and Practice of Hospital Medicine, 1st Edition, Sylvia C. McKean, Editor-in-Chief, McGraw-Hill publishers.
8. **Merlo CA.** "Diffuse Parenchymal Lung Disease." In Current Therapy in Thoracic and Cardiovascular Surgery. Mosby 2013.
9. **Merlo CA,** Terry PB. "Chest X-Ray Review". In The Johns Hopkins Internal Medical Board Review. Mosby. 2015

Letters, correspondence - None

Other Media - None

Teaching

Classroom instruction

- | | |
|--------------|---|
| 2003-2010 | Pulmonary physiology small group facilitator, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2003-2010 | Pulmonary pathophysiology small group facilitator, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2004-2010 | Good Samaritan Internal Medicine Program Guest Lectures – Cystic Fibrosis, Pulmonary Function Testing, Baltimore, MD. |
| 2004-present | Lecturer, Carol Johns Service (Inpatient Pulmonary Service) – Lecture monthly about Cystic Fibrosis and Lung Transplantation to medical students, residents, and fellows as part of the core curriculum on the inpatient pulmonary service, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2004-present | Lecturer, Pulmonary and Critical Care Medicine Fellow's Core Conference – Cystic Fibrosis, Lung Transplantation, Hereditary Hemorrhagic Telangiectasia, and Noninfectious Pulmonary Complications of HIV, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2006-2014 | Chest Radiography Conference Director – Lecture weekly for 10-15 Pulmonary and Critical Care Medicine fellows regarding the reading of chest radiographs and computed tomography, Johns Hopkins University School of Medicine, Baltimore, MD. |

Clinical Instruction

- | | |
|--------------|---|
| 2004-present | Medical Intensive Care Unit. Attending physician 4 to 6 weeks per year, Johns Hopkins. |
| 2004-present | Pulmonary Consultation Service. Attending physician four weeks per year, Johns Hopkins. |
| 2004-present | Lung Transplantation and Pulmonary Hypertension Service. Attending physician 8 weeks per year, Johns Hopkins. |
| 2004-present | Pulmonary Physiology Service. Attending physician four weeks per year, Johns Hopkins. |
| 2005-present | Janeway Firm Faculty. Teaching Attending 4 weeks per year, Johns Hopkins. |

CME Instruction

- | | |
|------|---|
| 5/06 | PFT interpretation, Topics/Tumulty Rounds, Johns Hopkins, Baltimore, MD. |
| 4/06 | Challenging infections among adults with cystic fibrosis. Medical Grand Rounds. Johns Hopkins, Baltimore, MD |
| 8/07 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Williamsburg VA. |
| 1/07 | Cough for the Allergist, Allergy Symposium, Bayview Medical Center, Baltimore, MD. |
| 7/08 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Bar Harbor ME. |
| 2/09 | Hereditary Hemorrhagic Telangiectasia- A Fresh Start to an Old Disease. Medical Grand Rounds. Johns Hopkins, Baltimore, MD. |
| 7/09 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Washington DC. |
| 1/10 | An update in Cystic Fibrosis, Allergy Lecture Series, Johns Hopkins, Baltimore, MD. |
| 4/12 | Nutritional Considerations after Lung Transplantation in Cystic Fibrosis. Nutrition Grand Rounds. Johns Hopkins, Baltimore, MD. |
| 9/12 | Hereditary Hemorrhagic Telangiectasia. Medical Grand Rounds. Johns Hopkins Bayview. Baltimore, MD. |
| 5/14 | A Curious Case of Hypoxemia, Topics/Tumulty Rounds, Johns Hopkins, Baltimore, MD. |

9/14 Creating a Common Language in Cystic Fibrosis to Improve Adherence, Lecturer, Med-IQ. www.med-iq.com/a/796

Workshops/ Seminars

5/08 Invited Lecturer, Observational Studies, Short Course in Epidemiology. American Thoracic Society, Toronto, ON.

10/09 Symposium Chairperson, Infectious Complications in Cystic Fibrosis. North American Cystic Fibrosis Conference, Minneapolis MN.

10/10 Symposium Chairperson, End Stage Lung Disease in CF: From Lung transplantation to Palliative Care, North American Cystic Fibrosis Conference, Baltimore, MD.

10/10 Invited Lecturer. Rise and Shine Workshop Management of Hemoptysis and Pneumothorax in Cystic Fibrosis. North American Cystic Fibrosis Conference, Baltimore, MD.

Mentoring

Advisees

2006-2010 Elliott Dasenbrook, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine Johns Hopkins University, currently Assistant Professor of Medicine at Case Western Reserve, Cleveland, OH.

2006-2010 Jeffrey Hoag, MD, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine at Drexel University, Philadelphia, PA.

2008-2011 Brad Drummond, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine, Johns Hopkins University, Baltimore MD.

2008-2012 Natalie West, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine at Johns Hopkins University, Baltimore, MD.

2009-2011 Eric Weiss, MD MPH, Master's of Public Health student at Johns Hopkins Bloomberg School of Public Health, currently Assistant Professor of Surgery (adjunct) at Columbia College of Physicians and Surgeons, New York, NY.

2010-2012 Jeremiah Allen, MD, Resident, Johns Hopkins University, currently Attending Cardiac Surgeon, Kaiser Permanente, San Francisco, CA.

2010-present Andrew Braun, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2011-2013 Timothy George, MD, Resident, Johns Hopkins University, currently Resident Surgeon at Johns Hopkins University, Baltimore, MD.

2011-2014 Arman Kilic, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2011-present Mark Jennings, MD, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2012-2016 Allison Lambert, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2012-2016 George Arnaoutakis, MD, Resident, Johns Hopkins University, currently Cardiac Surgery Fellow, University of Pennsylvania, Philadelphia, PA.

2014-present Joshua Grimm, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2014-present Linda Yin, Medical student, Johns Hopkins University, currently a medical student at Johns Hopkins University, Baltimore, MD.

2015-present Todd Crawford, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2015-present Trent Magruder, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

Educational Program Building/ Leadership

2006-present Course Director, Design of Clinical Studies, Johns Hopkins Bloomberg School of Public Health. This is an ongoing course available in the 2nd term each year through the Department of Epidemiology in the School of Public Health. It is part of a series of courses known formally together as the Science of

Clinical Investigation series. Together these courses convey the fundamentals of clinical research. In my capacity as director, I am responsible each year for the syllabus, lectures, homework assignments, and follow-up questions which arise during the 12-week class. The course has expanded over the years starting with a class size of about 6-8 to now over 40 per term and now includes physicians, nurses, administrators, and research coordinators.

2012-present Course Director, Distance Education Design of Clinical Studies, Johns Hopkins Bloomberg School of Public Health. This is a fully online version of the above course available through the Office of Distance Education in the 3rd term. Lectures, assignments, and quizzes are all available online. Live sessions accompany the online media. This course has also expanded from just a few to over 30 students per session.

Educational Extramural Funding (Current, Pending, Previous) - None

CLINICAL ACTIVITIES

Certification

Medical

1998	Medical License, Commonwealth of Virginia	0101057430	Inactive
1999	Medical License, District of Columbia	MD31720	Inactive
2004-present	Medical License, Maryland	D0061725	Active

Boards

2000	Diplomate, Internal Medicine, American Board of Internal Medicine
2003	Diplomate, Pulmonary Disease, American Board of Internal Medicine
2005	Diplomate, Critical Care Medicine, American Board of Internal Medicine

Clinical Responsibilities

2004-present	Medical Intensive Care Unit. Attending physician 4 to 6 weeks per year, JHH.
2004-present	Pulmonary Consultation Service. Attending physician four weeks per year, JHH.
2004-present	Lung Transplantation and Pulmonary Hypertension Service. Attending physician 8 weeks per year, JHH.
2004-present	Pulmonary Physiology Service. Attending physician four weeks per year, JHH.
2004-present	Attend in the Adult Cystic Fibrosis Clinic. One half day per week
2009-present	Attend in HHT Clinic. One half day per month
2011-present	Attend in the Lung Transplantation Clinic. One half day per week

Clinical Program Building/Leadership

2010-2018	Director, Johns Hopkins Hereditary Hemorrhagic Telangiectasia Center of Excellence. In my capacity, I am responsible for the coordination of multidisciplinary care for the patients with HHT that we care for at Johns Hopkins. Working in partnership with Sally Mitchell, MD, we created the Johns Hopkins HHT Center of Excellence in 2010, one of 17 such centers in the United States. The center now includes over 35 specialists from 15 Hopkins Departments and Divisions and has increased exponentially in size to include over 400 patients and family members. The team at Hopkins now consists of a nurse coordinator as well as specialists from nearly every division and department within the Hopkins system.
2015-present	Associate Program Director, Johns Hopkins Adult Cystic Fibrosis Center. In my capacity, I assist the Program and Center Director in the coordination of care guidelines and the delivery of clinical care in both the inpatient and outpatient settings, assist with coordination of clinical trials, and provide education to medical students, physicians, nurses, respiratory and physical therapists, nutritionists, social workers, patients, and family members regarding the multidisciplinary subspecialty care needed for patients with CF.

Clinical Extramural Funding (Current, Pending, Previous) - None

SYSTEM INNOVATION AND QUALITY IMPROVEMENT ACTIVITIES - None

ORGANIZATIONAL ACTIVITIES

Institutional Administrative Appointments

2003-2005 Educational Committee, Division of Pulmonary and Critical Care Medicine
 2005-present Faculty Recruitment Committee, Division of Pulmonary and Critical Care
 2014-present Assistant Director of Outpatient Services, Johns Hopkins Division of Pulmonary and Critical Care Medicine
 2015-present Associate Program Director, Adult Cystic Fibrosis Center, Johns Hopkins Cystic Fibrosis Center

Editorial Activities - Not Applicable

Journal Reviewer

2009-present Chest
 2009-present Journal of Heart and Lung Transplant
 2009-present Journal of Cystic Fibrosis
 2009-present European Respiratory Journal
 2009-present American Journal of Transplantation

Advisory Committees, Review Groups/Study Sections

2012-present Member, Cystic Fibrosis Foundation Grant review Committee

Professional Societies

2004-present Member, American Thoracic Society
 2004-present Member, American College of Chest Physicians
 2010-present Member, International Society for Heart and Lung Transplant

Conference Organizer, Session Chair - Not Applicable

Consultantships - Not Applicable

RECOGNITION

Awards, Honors

1999 Clinical Pearls Student Teaching Appreciation Award
 1999 The William P. Argy Memorial House Staff Award
 2000 Alpha Omega Alpha, Georgetown University
 2003 DC Thoracic Society Annual Conference Award
 2003 NIH Loan Repayment Program Award for Clinical Research
 2005 Janeway Firm Faculty
 2005 CHEST Foundation's Young Investigator Award
 2005 NIH Loan Repayment Program Award for Clinical Research
 2010 Fellows Teaching Award, Johns Hopkins

Invited Talks

Local/National/International

2005 Speaker, Medical Grand Rounds. Virginia Hospital Center. "The Care of Adults with Cystic Fibrosis". Arlington, VA
 2005 Speaker, Pulmonary Grand Rounds. The University of Pittsburgh. "The influence of environmental and genetic factors on outcomes in cystic fibrosis". Pittsburgh, PA.
 2007 Plenary Speaker, International Society for Heart and Lung Transplant. "The effect of the Lung Allocation Score (LAS) on survival after lung transplantation". San Francisco, CA.
 2008 Speaker, North American Cystic Fibrosis Conference. "The Impact of the LAS on Outcomes in CF". Orlando, FL.
 2008 Speaker, Mid Atlantic Thoracic Society Conference. "Adult Cystic Fibrosis". Richmond, VA.
 2009 Speaker, Hereditary Hemorrhagic Telangiectasia International Scientific Conference. "Quality of Life among Patients with Hereditary Hemorrhagic Telangiectasia". Santander, Spain.
 2010 Speaker/ Session Chair, Society for General Internal Medicine. "Research During Residency- Striking the Balance at Hopkins". Minneapolis, MN.

- 2010 Speaker/ Session Chair, North American Cystic Fibrosis Conference. "Lung Transplantation and Cystic Fibrosis". Baltimore, MD.
- 2010 Speaker, Pulmonary Grand Rounds. Brown University. "Hereditary Hemorrhagic Telangiectasia". Providence, RI.
- 2010 Speaker, 8th International Congress on Lung Transplantation. "Understanding and Dissecting the Lung Allocation Scoring System". Paris, France.
- 2012 Speaker, Medical Grand Rounds. Georgetown University Hospital. "Adult Cystic Fibrosis". Washington, DC.
- 2012 Speaker, 16th Annual HHT Patient and Family Day, HHT Foundation, "Understanding Screening for HHT." Orlando, FL.
- 2013 Speaker, American Thoracic Society. "Understanding and Dissecting the Lung Allocation Scoring System". Philadelphia, PA.
- 2013 Speaker, Cystic Fibrosis Conference Mexico. "Outcomes in Adults with Cystic Fibrosis". Mexico City, Mexico.
- 2013 Speaker, Hereditary Hemorrhagic Telangiectasia International Scientific Conference. "Minimal Clinical Important Difference in Epistaxis Severity Score in HHT". Cork, Ireland.
- 2014 Speaker, Medical Grand Rounds. Virginia Hospital Center. "Adult Cystic Fibrosis". Arlington, VA.

OTHER PROFESSIONAL ACCOMPLISHMENTS

- 2013 Washington Post. When should you start worrying about that lingering cough? Give it time. http://www.washingtonpost.com/national/health-science/when-should-you-start-worrying-about-that-lingering-cough-give-it-time/2013/12/20/1e615e9c-665d-11e3-ae56-22de072140a2_story.html
- 2013 Hopkins Medicine. For Lung Transplant, Researchers Surprised to Learn Bigger Appears to Be Better. http://www.hopkinsmedicine.org/news/media/releases/for_lung_transplant_researchers_surprised_to_learn_bigger_appears_to_be_better_
- 2014 Cover photograph entitled "A View of the Dome". Annals of the American Thoracic Society, Volume 11, Issue 5. <http://www.atsjournals.org/toc/annalsats/11/5>
- 2014 Johns Hopkins Health. Calming that cough. http://www.hopkinsmedicine.org/news/publications/johns_hopkins_health/fall_2014/calming_that_cough
- 2015 EurekAlert! Lung transplant patients in the UK fare better than publicly insured Americans. http://www.eurekalert.org/pub_releases/2015-03/jhm-ltp031915.php

APPENDIX B

APPENDIX B

List of Literature Review and Materials Considered by Dr. Christian Merlo

1. Abenhaim et al., *Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension*. (1996) 335(9) N Engl J Med 609
2. Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis*. (2018) 27 Eur J Cancer Prev 248
3. Booth et al., *Risk factors for ovarian cancer: a case-control study*. (1989) 60(4) Br J Cancer. 592
4. Centers for Disease Control & Prevention, *Principles of Epidemiology in Public Health Practice*, Third Edition, An Introduction to Applied Epidemiology and Biostatistics, Lesson 1: Introduction to Epidemiology, <https://www.cdc.gov/opphss/csels/dsepd/ss1978/lesson1/section1.html>
5. Chang & Risch., *Perineal talc exposure and risk of ovarian carcinoma*. (1997) 79(12) Cancer. 2396
6. Chen et al., *Risk factors for epithelial ovarian cancer in Beijing, China*. (1992) 21(1) Int J Epidemiol. 23
7. Cook et al., *Perineal powder exposure and the risk of ovarian cancer*. (1997) 145(5) Am J Epidemiol. 459
8. Cramer & Xu, *Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer*. (1995) 5 Ann Epidemiol. 310
9. Cramer et al., *Ovarian cancer and talc: a case-control study*. (1982) 50(2) Cancer 372
10. Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*. (2016) 27(3) Epidemiology 334
11. Cramer et al., *Genital talc exposure and risk of ovarian cancer*. (1999) 81(3) Int J Cancer. 351
12. Deposition of Anne McTiernan, M.D., Ph.D., Jan. 28, 2019 (MDL No. 2738)
13. Deposition of April Zambelli-Weiner, Ph.D., Jan. 11, 2019 (MDL No. 2738)
14. Deposition of April Zambelli-Weiner, Ph.D., Feb. 7, 2019 (MDL No. 2738)
15. Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738)
16. Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738)
17. Deposition of Jack Siemiatycki, Jan. 31, 2019 (MDL No. 2738)
18. Deposition of Rebecca Smith-Bindman, M.D., Feb. 7, 2019 (MDL No. 2738)
19. Deposition of Rebecca Smith-Bindman, M.D., Feb. 8, 2019 (MDL No. 2738)
20. Deposition of Patricia Moorman, M.S.P.H., Ph.D., Jan. 25, 2019 (MDL No. 2738)
21. Deposition of Sonal Singh, M.D., M.P.H., Jan. 16, 2019 (MDL No. 2738)
22. Doll & Hill, *The mortality of doctors in relation to their smoking habits*. (1954) 328 (7455) BMJ 1529
23. Expert Report of Anne McTiernan, M.D., Ph.D., Nov. 16, 2018 (MDL No. 2738)
24. Expert Report of April Zambelli-Weiner, Ph.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)
25. Expert Report of Ghassan Saed, Ph.D., Nov. 16, 2018 (MDL No. 2738)
26. Expert Report of Jack Siemiatycki, M.Sc., Ph.D., Nov. 16, 2018 (MDL No. 2738)
27. Expert Report of Patricia Moorman, M.S.P.H., Ph.D., Nov. 16, 2018 (MDL No. 2738)
28. Expert Report of Rebecca Smith-Bindman, M.D., Nov. 15, 2019 (MDL No. 2738)
29. Expert Report of Sonal Singh, M.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)

30. Gates et al., *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype*. (2010) 171 Am. J. Epidemiology 45
31. Gates et al., *Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer*. (2008) 17(9) Cancer Epidemiol Biomarkers 2436
32. Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249
33. Godard et al., *Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study*. (1998) 179(2) Am J Obstet Gynecol. 403
34. Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*. (2016) 27 Epidemiology 797
35. Green A, Purdie D, Bain C, et al., *Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group*. (1997) 71(6) Int J Cancer. 948
36. Grimes & Schultz, *Bias and causal associations in observational research*. (2002) 259(9302) Lancet 248
37. Gross & Berg, *A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer*. (1995) 5(2) J Expo Anal Environ Epidemiol. 181
38. Harlow & Weiss, *A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc*. (1989) 130(2) Am J Epidemiol. 390
39. Harlow et al., *Perineal exposure to talc and ovarian cancer risk*. (1992) 80(1) Obstet Gynecol. 19
40. Hartge & Stewart., *Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981*. (1994) 36(8) J Occup Med. 924
41. Hartge et al., *Talc and Ovarian Cancer*, (1983) 250 J. Am. Med. Ass'n 1844
42. Hill, *Environment and disease: association or causation?* (1965) 58 Proc Royal Soc Med. 295
43. Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*. (2014) 106(9) J Nat. Cancer Inst
44. Huncharek et al., *Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies*. (2003) 23 Anticancer Res. 1955
45. Huncharek et al., *Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies*. (2007) 18 Eur J Cancer Prev 422
46. Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Sever Childhood Diseases?* (2003) 157(2) Am J Epidemiol 176
47. Jordan et al., *Risk factors for benign, borderline and invasive mucinous ovarian tumors: Epidemiological evidence of a neoplastic continuum?* (2007) 107 Gynecol. Oncol. 223
48. Jordan et al., *Risk factors for benign serous and mucinous epithelial ovarian tumors*. (2007) 109(3) Obstet Gynecol. 647
49. Kurta et al., *Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case-Control Study*. (2012) 21(8) Cancer Epidemiol Biomarkers Prev. 1282
50. Langseth et al., *Perineal use of talc and risk of ovarian cancer*. (2008) 62 J Epidemiol Community Health 358
51. Malmberg et al., *Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development*. (2016) 468(6) Virchows Arch. 707-13
52. Merritt et al., *Talcum Powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer*. (2008) 122 Int'l J. Cancer 170

53. Mills et al., *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*. (2004) 112 Int'l J. Cancer 458
54. Moorman et al., *Ovarian Cancer Risk Factors in African-American and White Women*. (2009) 170(5) Am J Epidemiol 598
55. Narod, *Talc and ovarian cancer*. (2016) 141 Gynecol. Oncol. 410
56. Nat. Cancer Inst., *Cancer Stat Facts: Ovarian Cancer*, <https://seer.cancer.gov/statfacts/html/ovary.html>
57. Nat. Cancer Inst., *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ) – Health Professional Version*, https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#link/_220_toc (last updated Jan. 4, 2019)
58. Nat. Health & Medical Res. Council, *NHMRC Levels of Evidence and Grades for Recommendations for Developers of Clinical Practice Guidelines* (2009)
59. Ness et al., *Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer*. (2000) 11(2) Epidemiology 111
60. Oleckno, *Epidemiology: Concepts and Methods*. (2008)
61. Penninkilampi and Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*. (2018) 29(1) Epidemiology 41
62. Pike et al., *Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study*. (2004) 82(1) Fertil Steril. 186
63. Purdie et al., *Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study*. Survey of Women's Health Study Group. (1995) 62(6) Int J Cancer. 678
64. Rosenblatt et al., *Genital powder exposure and the risk of epithelial ovarian cancer*. (2011) 22 Cancer Causes Control 737
65. Rosenblatt et al., *Mineral Fiber Exposure and the Development of Ovarian Cancer*, (1992) 45 Gynecologic Oncology 20
66. Rosenblatt et al., *Characteristics of women who use perineal powders*. (1998) 92(5) Obstet Gynecol 753
67. Schildkraut et al., *Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)*. (2016) 25(10) Cancer Epidemiol Biomarkers Prev. 1411
68. Schlesselman, *Case-control studies: design, conduct, analysis* (1982)
69. Schultz & Grimes, *Case-control studies: research in reverse*. (2002) 359(9304) Lancet 431
70. Shushan et al., *Human menopausal gonadotropin and the risk of epithelial ovarian cancer**. (1996) 65(1) Fertil Steril. 13
71. Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*. (2013) 6(8) Cancer Prev Res 811
72. The Scandinavian Simvastatin Survival Study Group. *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction*. (1993) 71 Am J Cardiol 393
73. Tzonou et al., *Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer*. (1993) 55(3) Int J Cancer. 408
74. Vavken & Dorotka, *A Systematic Review of Conflicting Meta-Analyses in Orthopaedic Surgery*. (2009) 467(10) Clin Orthop Relat Res. 2723

75. Vetter & Mascha, *Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My!*, (2017) 125(3) *Anesth Analg* 1042
76. Wang et al., *Statistics in Medicine – Reporting of Subgroup Analyses in Clinical Trials*. (2007) 357(21) *N Engl J Med* 2189
77. Whittemore et. al., *Personal And Environmental Characteristics Related To Epithelial Ovarian Cancer*, (1988) 128 *Am J. Epidemiol* 1228
78. Wong et al. *Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study*. (1999) 93 *Obstet Gynecol* 372
79. Wu et al., *African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*. (2015) 24(7) *Cancer Epidemiol Biomarkers Prev.* 1094
80. Wu et al., *Markers of inflammation and risk of ovarian cancer in Los Angeles County*. (2009) 124 *Int'l J. Cancer* 1409
81. Wynder et al., *Radford Conference Report: Weak associations in epidemiology and their interpretation (3rd ed.)*. (1982) 11 *Prev. Med*

APPENDIX C

Fed. R. Civ. P. 26(a)(2)(B)(v) Disclosure for Christian Merlo, M.D., M.P.H.

Year	Parties	State	Caption
2015	Blevins v. Pyron	Missouri	Blevins v. Pyron Lawrence County Circuit Court 14LW-CC00108
2015	Grove v. UMMS	Maryland	Grove v. UMMS USDC Maryland 12-cv-2950
2015	Dutton v. UMMS	Maryland	Dutton v. UMMS Baltimore City Circuit Court 24-C-14-003848
2015	Hawkins v. Mercy Kansas	Missouri	Hawkins v. Mercy Kansas St. Louis City Circuit Court 1422-CC09810
2015	Whitehead v. CVS	Florida	Whitehead v. CVS Miami-Dade County Circuit Court 14-25980CA01
2016	Evans v. Livingston Health Care	Montana	Evans v. Livingston Health Care Gallatin County District Court DV-11-990B
2016	Moore v. Mercy	Maryland	Moore v. Mercy Baltimore City Circuit Court 24-C-16-004483
2016	Quintanilla v. Narayanan	Maryland	Quintanilla v Narayanan Montgomery County Circuit Court 397252V
2017	Burns v. Bowser	Virginia	Burns v. Bowser Virginia 13th Judicial Circuit CL14005484-00
2017	Monroe v. Franklin Square	Maryland	Monroe v. Franklin Square Baltimore County Circuit Court 03-C-16-001886
2017	Weisman v. Maryland General	Maryland	Weisman v. Maryland General Baltimore City Circuit Court 24-C-16-004199
2017	Almquist v. Kinsey	Maryland	Almquist v. Kinsey USDC Maryland 1:15cv292
2017	Sullivan v. Holy Cross	Maryland	Sullivan v. Holy Cross Montgomery County Circuit Court 423516v
2018	Flores v. Kaiser	Maryland	Flores v. Kaiser Montgomery County Circuit Court 427661v
2018	Hamlin-Lewis v. Guckes	Maryland	Hamlin-Lewis v. Guckes USDC Maryland 1:16cv3357
2018	Hirschenson v. Cleveland Clinic	Florida	Hirschenson v. Cleveland Clinic Broward County Circuit Court CACE13001180
2018	Knoerlein v. Express Primary Care	Maryland	Knoerlein v. Express Primary Care Baltimore County Circuit Court 03-C-17-001137
2018	McRae v. Dimensions Health	Maryland	McRae v. Dimensions Health Prince George's County Circuit Court CAL1702184
2018	Fluoroquinolone Liability Litigation	New Jersey	
2019	Jones v. Agrawal	Maryland	Jones vs Bon Secours Hospital Baltimore, Inc, et al ("Jones v. Agrawal") Baltimore County Circuit Court 24C18000398

Exhibit M

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
JACK SIEMIATYCKI MSc, PhD**

A handwritten signature in blue ink, reading "Siemiatycki".

Date: November 16, 2018

Jack Siemiatycki MSc, PhD

EXPERT REPORT OF JACK SIEMIATYCKI MSc, PhD
On
TALCUM POWDER USE AND OVARIAN CANCER

Jack Siemiatycki, MSc, PhD, FCAHS

106 Columbia Avenue

Westmount, Quebec, Canada

November 16, 2018

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1. My mandate

I have been retained to assess the epidemiologic evidence regarding the **general causation** between perineal (or genital) use of talcum powder products and risk of ovarian cancer. The question is: "Can application of talcum powder products in the perineal region cause ovarian cancer?"

All of my opinions in this report are stated to a reasonable degree of scientific certainty.

2. My credentials, expertise and experience

I am a tenured Professor of epidemiology at the University of Montreal and an Adjunct Professor of epidemiology at McGill University in Montreal. I have received prestigious national research awards in Canada, such as National Health Scientist Salary Award, Medical Research Council Distinguished Scientist Award, Canada Research Chair in Environment and Cancer and, currently, I hold the Guzzo-Cancer Research Society Chair in Environment and Cancer. I am an elected fellow of the Canadian Academy of Health Sciences. I was awarded a lifetime achievement award by the Canadian Society for Epidemiology and Biostatistics, the premier professional organisation in our discipline.

Trained in statistics and in epidemiology, I have devoted most of my research career to investigating links between environmental, occupational and lifestyle factors and various types of cancer. My research has been both substantive – namely, looking at particular factors and their possible relationship to particular cancers - and methodological – namely, exploring how to evaluate and enhance the validity of epidemiologic research through various prisms: study design, data collection methods and statistical analysis. Of my approximately 250 research publications, about one quarter would be considered to have methodological focus.

I have held various leadership positions, including the elected presidency of the Canadian Society for Epidemiology and Biostatistics, and elected membership on the Board of the American College of Epidemiology. I have been invited to serve on over 160 Boards, Scientific Councils and Expert Panels for a host of governments, universities or research agencies. Examples include: Board of Directors of the Canadian National Cancer Institute, member of expert panel tasked with recommending priorities for action under the

Canadian Environmental Protection Act, member of external peer review panel of the Epidemiology branch of the US National Cancer Institute (NCI), member of two different expert advisory bodies to research projects at the NCI, consulted by President Clinton's Cancer panel, member of external peer review panel for the Helmholtz German national medical research agency, Chair of the Scientific Council of the largest prospective study of causes of cancer being conducted in France, and others of that nature.

I have been associate editor of the American Journal of Epidemiology and the International Journal of Environmental Health. In addition, I have served as reviewer for about 20 journals. I have served as a chair and as a member of grant review panels for major Canadian scientific funding agencies.

My research programme has been well funded by Canadian funding agencies for over 35 years. I have conducted research and published on the carcinogenicity of a large number of agents in the occupational environment (e.g. asbestos, silica, welding fumes) and in the general environment (e.g. smoke from wood stoves, urban air pollution) and lifestyle factors (e.g. smoking, alcohol, use of cell phones).

I have taught and supervised epidemiology students and many of my former trainees are now faculty members in universities around the world.

I have had a long association with the International Agency for Research on Cancer (IARC). IARC is the premier institution in the world for cancer epidemiology and for environment and cancer research. It has several mandates, including the organisation and compilation of standardised high quality data on cancer incidence around the world, the conduct of original research, and the evaluation of the carcinogenicity of different agents with which humans come into contact. The latter is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens. Since the inception of this program in 1971, there have been about 120 meetings held and approximately 1100 agents have been evaluated.

A particular point of pride for me is that over the years, research results from my team have been cited as part of the information base on 69 of the 1100 agents that have been evaluated, probably making my team the most cited epidemiology team in the history of the IARC Monograph program.

My association with IARC began when I did a post-doctoral fellowship there in 1977-79. Over the intervening years I have collaborated with scientists at IARC on various research projects. I was a member of the 18-member Scientific Council of IARC from 2006 to 2010 including two years as elected Chairman of the Council. The Scientific Council oversees all of the scientific activities at IARC; its members are named by the member states of IARC. I have been invited to sit on IARC Monograph international expert panels for 5 of the 60 panels convened in the past 25 years. One of the IARC Monograph panels of which I was a member was tasked with evaluating: "Carbon black, titanium dioxide and non-asbestiform talc." Out of the 16 invited experts who participated in the meeting as members of the Working Group, I was selected to chair the meeting.

Subsequent to the IARC meeting and the report of the meeting, a small subgroup of members of the IARC Working Group, of which I was a member, conducted and published a meta-analysis of the results of the studies that had been available to the IARC Working Group (Langseth, 2008)

Although I have not personally produced original data collection studies on the topic, I am well qualified to review the epidemiologic evidence. I have participated in two published reviews of the issue. The methodologic expertise and analytical skills required to critically review and evaluate such evidence is generic to the vast area of environmental epidemiology of cancer. I am routinely asked by journals and grant agencies to provide expert opinions on topics for which I have not produced original data collection studies, but that are within the purview of my expertise. The invitation by IARC to chair the meeting at which talc was evaluated is testimony to the fact that my competence and expertise in this matter are internationally recognized by peers. I do not claim expertise in various adjoining domains that inform this issue, including physiology, pathology, clinical oncology, experimental toxicology, geology and mineral chemistry. However, I do have the

expertise and skill to assimilate information that is provided by experts in these areas. I have previously submitted a report on my review of the evidence regarding talcum powder products and ovarian cancer in October 2016.

I have previously served as an expert witness for plaintiffs in one U.S. court case, and that was a talc litigation in Los Angeles in 2017. (Eva Echeverria, BC628228, Johnson and Johnson Talcum Powder Cases, CA JCCP No. 4872), and I testified that the genital use of talcum powder products can cause ovarian cancer.

I have served as an expert witness in two Canadian court cases, neither having to do with talc or hygiene powders or ovarian cancer. One case dealt with a class action lawsuit on behalf of a town in Canada adjoining a Canadian military base where there had allegedly been a spill of trichloroethylene that seeped into the water table of the town. The residents claimed that the contamination had caused cases of cancer. I was an expert for the defence, the Canadian government, and I testified in 2012. (Province of Quebec Superior Court file 200-06-000038-037).

The other case was a class action on behalf of Quebec residents who contracted cancer and had been smokers, claiming that the tobacco companies were responsible for their diseases. I was an expert for the plaintiffs and I testified in 2014. (Province of Quebec Superior Court file 500-06-000076-980).

In my work as an expert for legal cases, my time is billed at the rate of \$450 per hour for research, report preparation, communications with counsel, participation in depositions, and testimony in court.

3. Overview of my methodology

The basis of my opinions derive from my education, training, experience, research and what is accepted within the community of leading scientists practicing in the field of epidemiology. My opinions are based on my review of the relevant materials, published in the scientific literature and/or produced in this case; including internal company documents, as well as relevant depositions, reports and testimony in the talcum powder product litigation. To reach my conclusions, I have employed the same scientific

methodology and rigor that I use in my research, in my publications and in the consulting and advising that I carry out on behalf of governments, public health agencies and research institutes. This includes a review of the relevant published literature, expert judgment to assess the quality and meaning of the various studies that were reviewed, and syntheses of the available evidence and any other pertinent medical and scientific evidence of which I am aware. The methods I used to derive and present my opinions are those used in general in the assessment of causal relations in medicine and public health, and more specifically in epidemiology. The methods are based on the experience and insight I have accumulated over 40 years of research, consulting, reviewing and student supervision, from discussions and interactions with leading epidemiologists, service on multiple IARC panels, and from reading evolving ideas in the scientific literature, including such seminal works as Bradford Hill's (Hill 1965) writings on assessing causality.

My opinions may be further supplemented and refined, subject to results that may come from further medical and scientific study and research and the continued review of additional information and discovery materials produced in this litigation.

4. The science of epidemiology

This section is designed to provide a non-specialist reader with information and definitions about epidemiology and biostatistics that are needed to understand the basis of my evaluation on talcum powder products and ovarian cancer. I do not present in this section the actual data and evidence regarding talcum powder products and ovarian cancer.

Epidemiology is the science of occurrence of diseases in human populations. It is concerned with the patterns of disease occurrence and also with identifying the factors that influence disease occurrence. These two sets of concerns are sometimes referred to respectively as descriptive epidemiology and analytic epidemiology. The first addresses such issues as the incidence of the disease in different geographic areas, in different time periods, or at different ages and sexes. The second addresses more focused questions on the specific environmental and/or lifestyle and/or genetic factors that might influence the incidence of disease.

The word “epidemiology” has the same etymologic roots as the word “epidemic”, which signifies that, initially, epidemiology grew out of the study of epidemics. Such epidemics were often of a microbial origin (e.g. viruses, bacteria, parasites). But increasingly in the 19th and especially in the 20th century, it became clear that the etiology (i.e. causation) of chronic diseases such as cancer could also be elucidated by studying their patterns of occurrence.

While there were many studies carried out in the early to mid-20th century that we would now qualify as epidemiological in nature, the discipline of epidemiology and its methods started to become formalized in the 1950’s and 1960’s. There are now departments of epidemiology in most large universities that have health science research and teaching activities and there are many national and international societies of epidemiology.

Epidemiology is characterized by its mainly observational and non-experimental approaches. It is a discipline that is not primarily based in the laboratory; rather it is based in society. That is the source of its strength, and its weakness. Because it deals with people in the reality of their lives, it is the most pertinent approach to understanding the links between people’s lifestyles and environments and their health and disease. However, because it is based in society, it by necessity confronts the extreme complexity of human lifestyles, environments and diseases. And because we cannot experiment with people’s lives, we cannot control the conditions in which people are exposed. The methods of epidemiologic research are complex and differ from study to study. Statistical methods play an important role in trying to tease out the role of different variables and in determining whether the observed results may be attributable to chance, to bias or to real effects of putative risk factors. It is usually necessary to assemble evidence from several data-collection studies on a given topic before being able to draw inferences about causality.

4.1 Some basic measures and notions used in epidemiology

In this section I will review a number of concepts that need to be understood in order to properly understand my review of the evidence regarding talc powder and ovarian cancer. It is intended for readers who may not be expert in epidemiology. In this section I will not necessarily tie the concepts and definitions to the talc-ovarian cancer issue; that part will

be left for later. For now, I am simply introducing the non-epidemiologist reader to terminology and concepts with which she/he may not be very familiar.

Prevalence of disease. The prevalence of a disease refers to the proportion of a population who are living with the disease at any given point in time.

Incidence of disease. The incidence of a disease refers to the proportion of a population who are newly diagnosed with the disease during a certain period of time. The bridge between incidence rate and prevalence rate is the average duration of the disease, or how long people live with it before they are cured or pass away. In fact, while incidence and prevalence are foundational concepts in epidemiology, it is only incidence that figures prominently in the evaluation of carcinogenicity of talc.

Risk of disease. The risk of disease is a term that can refer to incidence or prevalence. The meaning should be clear from the context in which it is used. For studies of cancer, it almost always refers to incidence of disease. This is the way I will use the term in this report.

“Cause” of disease. A cause of a disease is any agent or characteristic (environmental, lifestyle or genetic) that increases the probability of getting the disease or it may simply advance or hasten the onset of the disease. It may act alone or it may act in concert with other factors over a lifetime to cause the disease. It may act immediately (e.g., cyanide as a cause of poisoning; lack of seat belt use as a cause of car accident mortality) or it may take many years for the effect to become manifest (e.g., lack of physical activity as a cause of obesity). There may be many different causes for the same disease. (See explanation of Multifactorial Etiology below.)

Risk factor. As defined in the Dictionary of Epidemiology (Last 2001), a risk factor is an aspect of personal behavior or life-style, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with a health-related condition. The term *risk factor* is used rather loosely and depending on the context it can refer to a factor that directly causes a disease or a factor that is a strong marker for the proximal cause of the disease. As it is often used, I will

mainly use the term “risk factor” as a synonym for the noun “cause” of the disease. (eg. “Smoking is a risk factor for lung cancer.”)

Association. As defined in the Dictionary of Epidemiology (Last 2001), association refers to the degree of statistical dependence between two or more events or variables. Events are said to be associated when they occur more frequently together than one would expect by chance. Association does not necessarily imply a causal relationship.

Risk among unexposed (R_u) refers to the risk of disease among persons who are not (or were not) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have never* used talc in the perineal region.

Risk among exposed (R_e) refers to the risk of disease among persons who are (or were) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have* used talc in the perineal region.

Relative Risk: $RR = R_e/R_u$ = Risk among exposed/Risk among unexposed

When $RR > 1.0$, it indicates that exposure to the agent increases the risk of developing the disease. When $RR < 1.0$, it indicates that exposure to the agent prevents the disease.

When $RR = 1.0$, it indicates that the exposure to the agent has no bearing on the risk of getting the disease.

95% Confidence interval (95% CI). This refers to the precision of an estimate of a parameter. When we estimate the 95% CI for the RR, we are approximately saying that we are 95% certain that the true parameter underlying the study is within these limits. (The true interpretation is more subtle.)

Statistical significance of an association: Statistical significance is a measure of the departure of a set of data from some null hypothesis. Most commonly in epidemiology, the null hypothesis would state that there is no association between a factor and a disease. The null hypothesis can be operationalized in different ways, such as that the $RR = 1.0$, or that there is no trend between the degree of exposure and the RR. Once a study is conducted, the results can be compared with the expected results based on the null hypothesis, and the discrepancy from the null hypothesis is measurable with probabilities. This is done

either by computing a p-value or a confidence interval. If the p-value is very small or the confidence interval does not include the null value, then we say that an observed association between the putative risk factor and the disease is unlikely to be due to chance alone.

It is important to note that while statistical significance is a tool for assessing whether an observed association is attributable to chance alone, it is not a very effective tool for establishing the absence of an association. That is, the absence of statistical significance is not tantamount to proof of the absence of an association. The absence of statistical significance can be due to the true absence of an association, but it can also be due to the study not having sufficient statistical power or to bias or confounding in the research methods. Furthermore, it should be noted that the conventional dichotomization of results as “statistically significant” or not, based on a particular cutpoint on the p-value scale (eg. $p = 0.05$), is a gross simplification. The compatibility of the data with the null hypothesis of no association is in truth on a continuous scale and the dichotomization is arbitrary and potentially misleading, especially when the observed p-value is close to the arbitrary cutpoint.

In practice, epidemiologists have been moving away from using and reporting p-values and statistical significance, as it has become clear that the main contribution of an individual study is to provide an estimate of the relative risk and its range of plausible values, embodied in a confidence interval.

Cohort studies and case-control studies: Epidemiologic research projects can take many different forms. The two most common types of analytic epidemiologic studies are cohort studies and case-control studies. (Rothman, Greenland, & Lash 2008)

In a cohort study, it is typical to enrol a large number of subjects, determine which ones are or have been exposed to the factor of interest (e.g., talc) and follow them for some period of time to evaluate whether those who were exposed subsequently experienced different disease rates from those who were not exposed.

In a case-control study, by contrast, we start with people who have the disease under study (e.g. ovarian cancer) and a set of controls who do not have the disease, and we collect data

to determine whether the cases and the controls had different histories of exposure to the factor under study (e.g. talc).

It may be said that a cohort study proceeds from the cause to the effect, whereas a case-control study starts from the effect and backtracks to the cause. There are many variants on these basic designs. These descriptions of these types of study are somewhat simplified.

It is sometimes claimed that a prospective cohort design produces more valid and reliable RR estimates than a case-control study. But this is incorrect as a generalization. The validity and reliability are not determined by the overall architecture of the study, but rather by the specifics of the study, including how the study subjects were assembled, the nature of the variables under study (exposure, disease, confounders), exactly how the information was collected, the statistical power, and so on. There may be many reasons why a particular case-control study is more valid than a particular cohort study.

Relative Risk (RR) and Odds Ratio (OR). The cohort study design leads naturally to the estimation of risk of disease among exposed, and risk of disease among unexposed, and then to the ratio of those two, which is the RR. In case-control studies, because of the way the study samples are selected, it is impossible to estimate the risk of disease or the ratio of the two risks, R_e/R_u . However, under certain conditions which are well met in studies of cancer, it is possible to estimate an approximation of the RR. This is called the odds ratio, referred to as OR. In the rest of this report, I will consider evidence obtained from both cohort studies and case-control studies, and I will refer to the findings of these studies as RRs, even if technically speaking, the results from case-control studies are ORs.

Bias, confounding, effect modification. The aim in an epidemiologic investigation of a putative risk factor is to derive an accurate estimate of the RR between exposure to the agent and the disease at issue. Because the investigator does not control the conditions in which people live and are exposed to different agents and their willingness to participate in research, there are many potential sources of distortion in epidemiologic research. While there are many sources of distortion, they can be bundled into a few large families of sources of distortion.

Bias refers to a systematic distortion in study findings, resulting from the way the study was designed or the way the data are collected. Specific examples of types of bias will be discussed below as they pertain to talc and ovarian cancer.

Confounding is sometimes considered to be a type of bias, and sometimes it is considered a type of distortion on its own. This is merely a semantic distinction. Confounding refers to the situation where the association under study between factor F and disease D is distorted because there is a third factor X which happens to be correlated with F and which is a cause of disease D. For instance if we want to study the association between occupational exposure to talc in mines (factor F) and lung cancer (disease D), we need to be mindful of whether cigarette smoking (factor X) is more common in talc miners than in the rest of the population. Confounding differs from other types of bias in that it depends on relationships among different variables in the population, rather than characteristics of the study design and data collection.

Effect modification refers to the phenomenon whereby a given factor has a different effect in one sub-population than in another. If we study the association between that factor and the disease in the entire population without distinguishing the two sub-populations, we might end up with an estimate of the association that does not convey accurately the association in either sub-population. For instance, if it were the case that a certain genetic characteristic G increases the risk of pre-menopausal ovarian cancer but has no impact on post-menopausal ovarian cancer, then a study of the association between G and ovarian cancer that does not discriminate by menopausal status, would find an RR result somewhere between the null value among post-menopausal women and the true RR value among pre-menopausal women. Depending on the proportions of pre- and post-menopausal women in the sample, the overall RR might be so close to the null, that we might erroneously conclude that there is no association at all. In this example, it might actually be quite simple to detect the effect modification, since age is always recorded and menopausal status is usually recorded and investigators are sensitized to the possible effect modification of female cancers by hormonal status. Other potential effect modifiers may not be so easily available and they might not be on the radar screens of investigators. Effect modification can in some unusual circumstances completely wipe out a true causal

association (as when the agent causes cancer in some people but prevents cancer in others!). But generally, if there is a causal effect of the agent in one stratum of the population and no association in another stratum, and if we fail to stratify the population according to the effect modifier, it will have the effect of producing an overall RR that is lower than it truly is in the sensitive stratum and higher than it truly is in the insensitive stratum.

Effect modification is closely related to and sometimes synonymous with interaction or synergism.

Publication bias refers to the tendency for some evidence never to “see the light of day”. Namely, when results are “negative” or “null”, it may be that investigators never bother to submit them for publication, or alternatively that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small.

In this section I have briefly outlined some potential sources of distortion of a typical epidemiologic study. I have done this in a high-level generic way. Below, after presenting results of my review of pertinent literature on powders and ovarian cancer I will return to commenting on the possible impact of such distortions in this body of literature.

Exposure variable and exposure metric

An **exposure variable** can be anything that can influence the occurrence or outcome of disease. The term is used for such disparate entities as external components of what we eat, drink, breathe, hear or see and microbiological organisms, chemicals or forms of radiation.

Depending on the nature of the variable, information on an exposure variable can often be ascertained from epidemiologic study participants by questioning them. This is the case for variables like cigarette smoking or use of talc powders. For some variables, like exposure to a virus or to specific air pollutants or occupational chemicals, it is usually necessary to invoke more intensive data collection methods to ascertain exposure.

An ***exposure metric*** signifies a way of defining a variable for statistical analysis. The simplest metric is a binary variable: exposed or unexposed. For most exposure variables, like exposure to talc powder, there can be a very wide range of degree of exposure. And it is pertinent to create more nuanced exposure metrics that take into account the degree of exposure that different people have experienced, metrics such as duration of exposure, intensity or frequency of exposure and even cumulative measures of exposure over long periods of time.

Measurement error. Whenever we are measuring a variable in an epidemiologic study, be it smoking, or weight, or socio-economic status, or blood pressure, or any other variable, it is virtually inevitable that there will be some degree of error in the measurement. There are ways of collecting data that make them more or less likely to involve error, but it is almost impossible to ensure that variables are measured with perfect validity and precision. Even such a variable as the diagnosis of ovarian cancer is subject to differences of opinion among pathologists and oncologists and the presence or absence and the histologic type of tumour is not a guaranteed 100% perfect diagnosis. The ascertainment of the lifetime history of talc exposure by means of an interview with a woman in middle age or later in life is certainly susceptible to the caprices of memory and the way the questions are formulated may influence the validity of respondents' reports of lifetime exposure patterns. It is likely that habits that were performed regularly are more reliably recalled than activities that were sporadic or that only occurred many decades earlier. Similar issues arise for all other variables collected in such studies. We refer to measurement error as random (or non-differential) if the degree of measurement error does not differ between cases and controls in case-control studies or between exposed and unexposed in cohort studies. As a general rule of thumb, it can be asserted that random (or non-differential) measurement error has a predictable distorting effect on the RR. Namely, while there are some rather obscure exceptions, non-differential measurement error tends to attenuate the RR towards the null value of 1.0, and the more measurement error, the greater the attenuation. A full explanation for why this is so is quite technical and can be found in advanced epidemiology textbooks, such as Rothman, Greenland and Lash 2008. A very simple explanation is that the presence of measurement error in assigning exposed vs

unexposed status leads to dilution of both the exposed group and the unexposed group. That is, the ostensible exposed group (i.e. the folks who will be labelled as exposed based on the study data collection) will contain some folks who are truly unexposed and the ostensible unexposed group will contain some folks who are truly exposed. If there really is a difference in risk between the true exposed group and the true unexposed group, this difference will be watered down by the inadvertent inclusion in each group of folks who are really in the opposite group. An analogy is the cross-contamination of two cans of paint. Suppose we have a can of pure white paint and a can of pure red paint. Suppose we have a way of quantifying the difference in color tone between the two paints. Then suppose we take some spoonfuls from the red can and pour them into the white can, and likewise take a few spoonfuls of the white paint and pour them into the red can. Now the color contrast between the two cans has been attenuated. The color contrast in this example is like the relative risk in an epidemiological study which has been attenuated because the exposed and unexposed groups have been cross-contaminated.

Dose-response. It is important not only to assess whether there is an association between a variable and a disease when the variable is defined in a binary (exposed vs unexposed) way, but also when the variable is defined in a quantitative or semi-quantitative way. When we analyse the risk as a function of the degree or duration or intensity of exposure, we refer to this as a dose-response (or exposure-response) analysis. The example of the smoking and lung cancer is instructive about the value of different metrics, though it cannot be assumed that all risk factors act the same way. Studies using the binary metric for smoking (smoker/non-smoker) have been very consistent and persuasive in demonstrating an association between smoking and lung cancer. Further, when data are collected and analysed regarding the degree of smoking, it becomes clear that there is a monotonic dose-response relationship. That is, the more smoking, the higher the risk. And the quantitative metric that manifests the strongest association with lung cancer is the cumulative amount smoked over the lifetime. This is perfectly logical. Since the cumulative exposure metric embodies information on duration and on intensity, it can hardly be less predictive of risk than either of the dimensions alone.

We cannot assume that there is a universal form of a dose-response relationship for every true causal relationship. Most commonly, in toxicology and epidemiology, the relationship between exposure and risk is monotonic; that is, as one increases, so does the other. This can include linear relationships (i.e. where a straight line on a graph describes the relationship) or exponential or many other curvilinear forms. It is also possible that there may be a threshold effect (the risk only becomes apparent after a certain level of effective exposure) or some other non-standard relationship.

Both the qualitative metrics (ever/never) and quantitative metrics (a lot of use compared with a little use) are valid and useful metrics.

Sample size refers to the number of participants in the study. As a generalization, large studies produce more statistically stable and precise estimates than small studies. In fact the stability of estimates or precision of estimates is not a simple function of the number of participants, or subjects, in a study. The precision of estimates depends, among other things, on the type of epidemiologic design.

In a case-control study the main determinants are the numbers of cases and controls and the prevalence of exposure in the two groups; in a cohort study the main determinants are the numbers of participants, prevalence of exposure, and the incidence of the disease of interest over the period of follow-up in the exposed and unexposed groups.

There is sometimes confusion about the notion of sample size when we compare cohort studies with case-control studies. The operational aspect of an epidemiologic study of cancer that most influences the precision of an estimate of RR is not the total number of participants; rather, it is the smaller number between the number of exposed cases of disease and the number of unexposed cases. In a typical prospective cohort study, one might need to enroll 100,000 participants in order to end up with a certain number of cases (say, 500 cases) of the disease of interest (e.g. ovarian cancer). In a case-control design we might only need to enroll around 500 cases and 1500 controls to achieve the same statistical power as would be achieved by a cohort study of 100,000. The formal justification for this assertion is quite mathematical, and has to do with the fact that a sample of a population can give very accurate estimates of the characteristics of an entire

population. Thus, the simple comparison of 100,000 participants in a cohort study and 2,000 participants in a case-control study is in no way a valid marker for the relative statistical power of the two hypothetical studies. There are admittedly other advantages and disadvantages of the cohort vs the case-control design, and reviewers should consider the various aspects before deciding on the relative weight to give to the results of the different studies. But it is definitely not appropriate to merely compare the numbers of participants as an indicator of study validity.

While precision is based on multiple factors and different ones in case-control and cohort studies, there is a parameter which embodies the different factors quite well, and which is common to both case-control and cohort studies, namely, the number of exposed cases. For this reason, in laying out the various study results below, in addition to the relative risk estimates and their confidence intervals, I will show the numbers of exposed cases.

While it may affect the precision of estimates of RR, the size of the study does not in itself systematically affect the estimates of RR. That is, it is not the case that small studies produce systematically exaggerated RR estimates or systematically low RR estimates. However small studies can produce more wildly divergent RR estimates than large ones, in either direction, towards the null or away from the null.

Meta-analysis and pooled analysis: There are two distinct ways that evidence from multiple studies can be combined to derive a new overall statistical summary or synthesis of those studies, a meta-analysis and a pooled analysis. A meta-analysis uses the published results from each study and averages those results using some optimal weighting procedures. In order to implement a meta-analysis it is necessary to find all relevant studies on a topic that have published results in a fairly standardized way. The statistical algorithms typically used to average the results from different studies also provide statistics that evaluate how heterogeneous are the results from the different studies. The interpretation of such heterogeneity statistics is not straightforward. If the results from different studies are homogeneous, it adds to the confidence in the meta-estimate. If they are heterogeneous, it may indicate that the association is really different in different populations, or that there are some methodological characteristics of the different studies

that have influenced the results in different ways. Unless a significant methodological flaw can be identified that has caused the heterogeneity, the best overall estimate remains the meta-estimate.

A pooled analysis is one in which the investigator gets access not only to the published results from different studies, but rather to the individual data of every person in the studies. The latter is harder to achieve because it requires high buy-in and input from the investigators of the original studies; a meta-analysis is much easier to organise. Because a pooled analysis allows for standardization in the definition of variables and statistical models, it can be a more powerful means of summarizing data than the original studies themselves.

Multifactorial etiology of disease. Chronic diseases such as cancer are multifactorial in two distinct ways. On the one hand, each case of disease results from the unfortunate conjuncture of a combination of factors (these might include for example, genetic predisposition, diet, environmental pollutant, occupational exposure, medical intervention, viral infection, lifestyle habits, etc.) which combine over a lifetime to initiate and promote development of the disease. In this sense, each of the factors that are part of the combination for that person was a necessary contributor to the disease process, although it was not sufficient on its own to provoke the disease. Despite the fact that none of the factors were sufficient to produce the disease on their own, each of the contributory factors may be considered to be a cause of the disease. The disease would not have arisen if any of the contributory factors had been absent. This is one meaning of the multifactorial etiology of disease.

The second meaning is that the combination of factors that induce cancer in one person may not be the same as the combination that induces cancer in another person. Indeed, at the population level, there may be many combinations of causal factors for the same disease. Some factors may be common to different combinations. For example, it may be that in one case of lung cancer, the combination of factors included genetics, exposure to air pollution, exposure to radon in the home, and smoking; while in another person, the

combination of factors included genetics, insufficient dietary consumption of anti-oxidants like carotene, exposure to asbestos, and smoking.

Some characteristics of carcinogens and epidemiologic research on cancer: The following characteristics of most known carcinogens provide a framework for some of the thinking behind the design and interpretation of epidemiologic studies of cancer.

- There is typically a long induction period between exposure to a carcinogen and appearance of the disease. Thus, if a study has not allowed for a sufficient passage of time between the exposure and the disease, the result may report that there is no risk, where in fact there is a risk, but insufficient time has elapsed to make the risk visible.
- There is variability in the carcinogenic potency of different carcinogenic agents; some induce much greater relative risks than others.
- For any given carcinogen, the degree of risk due to exposure generally increases as the exposure level increases, but the shape of the dose-response curve may differ from one carcinogen to another.
- Most known human carcinogens were first discovered as such either by means of astute observation of a clinician noticing a cluster of cases among people who shared a common characteristic (such as working in a particular workplace) or by means of epidemiological research. In most cases, there was no known mechanism to explain the association at the time. Where the mechanisms have been elucidated, they were usually discovered subsequent to the epidemiologic demonstration of a causal relationship. (Siemiatycki 2014)

4.2 *Bradford Hill “guidelines”*

Because of the complexities of epidemiologic research, there has been some concern with how epidemiologic evidence should be used to draw causal inferences. Various authors have written about the types of information that might be considered in assessing whether a body of evidence demonstrates a causal relationship. A set of guidelines, developed in the context of the Surgeon-General’s Report on Smoking and Health (1964) and authored by

Bradford Hill in 1965, has achieved a wide consensus in the epidemiologic community as a pedagogical guide. Hill himself referred to these guidelines as “aspects” or “features” or “characteristics” of an association, and warned against treating them as “hard-and-fast rules of evidence that must be obeyed”. (Hill, 1965) He deliberately avoided referring to them as “criteria.”

Since Hill wrote those thoughts at the beginning of the era of modern epidemiology, without the benefit of decades of practical experience in the way those thoughts were taken up, and how they applied to issues other than smoking and cancer, it is understandable that the practice of evaluation of causality has evolved. A first observation, often overlooked, is that Hill took as a starting point for his writings that chance had been considered as an explanation for the smoking-cancer association and determined to be unlikely. In the historic context of 1964-1965 and the debates around smoking and cancer, this was a reasonable assumption to make, but for any other putative associations, this must be considered. Over the years, respected authors have paraphrased and updated these aspects in various ways, and this will undoubtedly continue. For instance, leading textbooks of epidemiology as well as the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) all have different formulations of Hill’s guidelines.

In the light of 50 years of practical experience after these guidelines were written, and based on my practical experience of evaluating causality in many forums and on many topics, I would paraphrase (and modernize) Hill’s guidelines as follows:

Strength of the association: This can be measured by different parameters, but for cancer studies it is usually measured by the magnitude of the relative risk or odds ratio.

Statistical significance of the association: While this guideline was not explicitly listed by Hill, it is nonetheless in practice an implicit and distinct consideration in assessing causality. If the estimated RR is quite high, indicating a strong association, but is based on a very small study with low precision, this might be solely due to statistical variability. (For instance, when we flip a balanced coin 10 times, we do not always end up with 5 heads and 5 tails. Sometimes, by chance, we may end up with 6 heads and 4 tails. Does this prove that the coin was not balanced?) Evaluating the role of statistical chance as a possible

explanation of the observed association is important. As explained above, the absence of statistical significance is not strong evidence of an absence of a real relationship.

Dose-response relation: If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. There are some counter-examples however where the effect is only observed after a threshold of exposure has been crossed. There are various ways to assess whether there is a dose-response relation. Hill pointed out that the main challenge is to establish reliable and measurable quantification of exposure. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency).

Absence of bias: There are many forms of bias that can infiltrate an epidemiologic study. It enhances the likelihood of a true causal association if we can confidently exclude all the plausible sources of bias explanations for the observed findings. This guideline can also be considered as a component of a guideline to consider other possible explanations for the association.

Temporality: It is clear that the exposure should precede the outcome (i.e. the disease). To ascertain whether the cancer was a result of the exposure or the exposure occurred after the cancer onset seems like a simple thing, but sometimes it can be difficult to ascertain with certainty.

Cessation of exposure: It would add to the credibility of the association if it had been demonstrated that subjects who cease exposure to the agent experience reduced risks of disease compared with those who continue to be exposed. In practice this is an extremely difficult characteristic to demonstrate, partly because of the difficulty or even ethical impossibility of changing people's habits for scientific experimentation purposes. But occasionally there may be a "natural experiment" wherein large numbers of people cease their exposure and the effects can subsequently be measured in an epidemiologic fashion.

Specificity of the association: It was believed that individual risk factors have specific pathological effects, and Hill posited that if we observe that a given agent is associated with

many different pathologies, it increases the likelihood that these are somehow spurious observations, resting on some type of bias in the studies of that agent. In reality, this Hill characteristic has fallen out of usage in the intervening years with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

Consistency of findings between studies (or replication of findings): Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship.

Coherence with other types of evidence: In the case of tobacco and cancer, it was seen that the historic trend in lung cancer mortality rates in the US and UK followed quite closely the national trends in consumption of tobacco, with a 20 year lag. This was interpreted by Hill as corroboration of the results observed in case-control and cohort studies. Epidemiologic evidence of coherence could conceivably take many forms, and the opportunity to assess coherence is something that is specific to the factor under investigation. Assessment of coherence with historic mortality trends would only be possible in the case of a factor whose exposure in the population changed quite dramatically over time in a way that can be documented, and for which the attributable fraction of the disease due to that factor is very high. This was the “perfect storm” of circumstances that allowed for an assessment of the tobacco-lung cancer association by means of time trend correlations.

Analogy: Hill reasoned that if a factor is somehow similar to another factor that has already been shown to be a risk factor for the disease, then it increases the plausibility of a similar impact due to that putative factor. This is such a vague guideline, with no clear implementation suggestions, that it is not often referred to and rarely implemented.

Biologic plausibility: This guideline can encompass many dimensions of information, including physiology (can the agent or its metabolites reach the organ?), animal carcinogenesis (does the agent produce tumours in experimental animals?), cell studies that reveal mechanistic data, and other biologic information on the toxicology of the agent.

Implementing Hill's guidelines: As Hill himself insisted, sophisticated users of these guidelines do not use them as a formal checklist. He summarized his views as follows:

« What I do not believe ... is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? »

The authors of the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) clearly stated that Hill's guidelines are not formal criteria, but rather are more in the nature of a memory aid to help us review the evidence about any given causal association. They stated it this way: "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines."

I have served on many panels to review evidence of causality on one topic or another, including on several IARC Monograph panels that reviewed evidence of carcinogenicity. The IARC process, like the others I have participated in, does not use the Hill guidelines in any rigid formal way. The ideas embodied in Hill's guidelines permeate our thinking about how to evaluate causality, but the operationalization of these guidelines is specific to the problem and to the expert making these determinations. Thus any suggestion that Hill's "aspects" or "features" or "characteristics" of an association should be used as a formal checklist of criteria is simplistic and wrong. To do so would contradict the opinions of experienced epidemiologists, the Manual on Scientific Evidence, and Bradford Hill himself.

In this section, I have laid out and explained the Bradford Hill guidelines in a generic way. Below, in section 8, I will consider how these apply in the context of the talcum powder – ovarian cancer issue.

5. Epidemiologic evidence regarding talc and ovarian cancer

Following some reports in the early 1980's that raised questions about a possible link between use of cosmetic talc powder by women and the risk of ovarian cancer, there were several epidemiologic studies on the topic. By the early 2000's the issue was garnering some attention in the scientific community. The International Agency for Research on Cancer, the premier agency for evaluation of carcinogens, decided to conduct a review of the issue in 2006. Following that review, there have been further studies conducted on the topic.

In the context of a legal action, my mandate is to review all relevant scientific evidence available to date, in order to provide the court with my opinion regarding the link between talc powder exposure and ovarian cancer. The methodology I employed is the same one I have used in my career as an internationally recognized researcher.

5.1 IARC review and evaluation of talcum powder products

As mentioned above in Section 2, the International Agency for Research on Cancer (IARC) is the premier institution in the world for cancer epidemiology and for environment and cancer research. One of its mandates is the evaluation of the carcinogenicity of different agents with which humans come into contact, and this mandate is carried out by the Monograph Programme of IARC. This is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens.

In February 2006, there was such an IARC Monograph meeting to evaluate some agents, including talc. The IARC Working Group comprised 16 highly respected and recognized scientists from around the world; I was asked to Chair the Working Group. We reviewed all

the evidence that was available up to that point in time. This certainly included epidemiologic evidence, but it also included evidence from experimental toxicology, physiology, molecular biology and other domains. The IARC Monograph programme has a formal system for classifying agents. The Working Group must classify an agent into one of the following categories:

- 1 Carcinogen
- 2A Probable carcinogen
- 2B Possible carcinogen
- 3 Not classifiable
- 4 Not carcinogen

After reviewing the evidence, the panel concluded that talc was a “possible carcinogen”, based primarily on evidence regarding the association between dusting powders and ovarian cancer. Here is the definition of this category from the IARC Monograph:

“Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals.”

This 2B categorization was based on the panel’s decision that there was “limited evidence of carcinogenicity in humans”, which is in turn defined by IARC as follows:

“Limited evidence of carcinogenicity in humans: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.”

Subsequent to the completion of the IARC Monograph on talc, a subgroup of the epidemiologists who were on the IARC Working Group, including myself, reviewed the evidence again, but with a view to producing a meta-analysis of the results from the most informative studies conducted to that time. This resulted in the paper by Langseth et al. (2008). This paper was not an IARC publication.

5.2 Information consulted for the present review

In preparation for formulating my current opinions on this topic I assessed, researched, reviewed and consulted a large number of documents, including, but not limited to: all original epidemiological studies published on this topic, all meta-analyses and opinion pieces, experimental toxicology, molecular biology, mechanistic studies, and the IARC Monograph on talc which reviewed all informative studies that had been published before 2006. I was given access to and also reviewed the various expert reports and depositions that have been submitted in various talc cases, either on behalf of the Plaintiff or Defendant, and various internal company documents obtained in discovery.

I systematically reviewed the lists of references of all relevant studies referenced in the IARC report as well as in various meta-analyses and in all recent articles on the topic to identify yet more relevant publications on talc and cancer.

Because some studies have been published in multiple papers and because some papers have included reports on multiple studies, there is not a one-to-one relationship between studies and published papers.

Additionally, I considered evidence regarding the toxicology of talc by reviewing the toxicology evaluation conducted by the IARC Working Group, the summary of talc's putative toxicology referenced in various scientific publications, and the expert reports of various scientific/medical experts in this case.

The central focus of my review is on the epidemiologic evidence.

A complete listing of the documents I consulted, as well as references cited explicitly in this report, is provided in the Bibliography. The Bibliography is in two Parts; Part A comprises all the publications and reports that can be found in publicly available scientific literature. Part B comprises company documents or documents from reports or testimonies of experts.

5.3 My methodology for this review

Table 1 lists the steps I undertook to accomplish my mandate.

5.3.1 Selecting studies for review

To aid in the present assessment of whether or not there is a causal relationship between talcum powder exposure and ovarian cancer, I carried out an up-to-date review of the scientific literature, primarily the epidemiologic literature, concerning the association between use of talc powder and risk of ovarian cancer. This involved meta-analyses to estimate the effect of having ever used perineal powdering, and an assessment of evidence regarding dose-response.

The first task was to find the relevant publications and to set out the distinct pieces of epidemiologic evidence, namely the results of different studies. Based on a number of reviews on the topic of talc and ovarian cancer, including the IARC report, I systematically went through the reference lists to identify all publications that seemed to contain results on the topic. I further conducted a Pubmed search and this did not produce any new informative publications that had not already been identified. In preparation of the meta-analysis, I eliminated from consideration papers that were outside the bounds of what a meta-analysis should contain (i.e. eliminate review articles, commentaries, meta-analyses, and articles that do not really pertain to the issue of perineal talc and ovarian cancer). From the 40 publications that remained, namely those that contained original results on the association between powdering and ovarian cancer, I extracted all results showing RRs between talc powdering and ovarian cancer, and I had these results put into a Filemaker database. This was a value-free exercise. I made no judgement at that stage about relevance or quality of the study or the published results. It was only an attempt to lay out in one “place” the whole of the evidence and to prepare for subsequent analyses. There were over 730 results in this database. On average each publication contained about 18 different RR results of various aspects of talc powder exposure and various types of ovarian cancer. Some contained fewer and some contained many more. (For instance, one study publication contained 180 results, with varying types of ovarian cancer and varying definitions of exposure to powdering.)

In deciding which results to include in a meta-analysis I had to respect the following principles:

- The results have to pertain to the issue of risk of ovarian cancer in relation to use of talc-based powders.
- Where there are sufficient numbers of results to support meta-analyses, there can be meta-analyses for different types of ovarian cancer, and for different routes of exposure to talc-powders.
- In each meta-analysis, each study should only provide one result, so as to avoid double-counting evidence.
- The decision about inclusion of a study should in no way be influenced by whether or not a particular study demonstrated high risks or low risks.

While these seem like simple principles to respect, there were complicating features of the scientific literature:

- Some studies were reported in multiple publications, sometimes the same study subjects were analysed and reported in different ways and sometimes different subsets of the study population were included in different publications. Sometimes the authors fail to clearly enunciate how the data used in one of their papers overlaps with data used in another of their papers from the same study.
- Different studies used different questions about powder use in their questionnaires, and sometimes the same study reported results by different ways of asking about or defining exposure.
- A given study may have presented one result or many results, each addressing a different definition of the talc exposure variable and different way of grouping the ovarian cancer cases.
- Different studies dealt differently with the histologic sub-types of ovarian cancer, sometimes grouping them all, or sometimes separating them, or sometimes reporting both grouped and separate results for different sub-types.

- Different studies used different metrics for analysing powder exposure and estimating its corresponding RR.
- Different studies dealt differently with the challenge of adjusting powder-related risks for possible confounding by other factors.

Decisions had to be made regarding which types of exposure to consider, which types of ovarian cancer to consider, which metrics of exposure to consider and which studies and publications to consider. It is necessary to be rigorous in making such decisions ahead of time, rather than “cherry-picking” results from different studies that appear to support one theory or another.

Appendix Table A1 provides a list of those 40 publicly available publications that have included some original results that might pertain to the association between powdering and ovarian cancer. **Appendix Table A1** shows which publications were included and which papers were excluded from my meta-analyses. For each of the 14 excluded papers, the table also shows the reason. Some papers were excluded because the results did not pertain to ovarian cancer and powdering in the perineal region. Some papers were excluded because the results presented therein were subsumed by a subsequent publication by the same research team or as part of a pooled analysis of multiple studies. Notwithstanding my intention to identify all unique studies and to extract a best “bottom line” result from each study, the nature of the studies and how they were analysed and reported led to many judgement calls. It must be acknowledged that there can be differences of opinion among equally competent and equally well-motivated scientists in how to choose among the different publications and the different results within publications.

Fortuitously, and unbeknownst to me at the time, two other sets of investigators (Berge et al 2018; Penninkilampi et al 2018) carried out separate meta-analyses on this topic at about the same time as I was carrying out mine, and this gives an opportunity to do some cross-comparison of different reviews and meta-analyses. I will comment on these after presenting the results of my meta-analyses.

5.3.2 What were women exposed to in body powders?

Talc has been the main ingredient of body powders used by women over the past century. “Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibers ... Talc may also form as true mineral fibers that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a ‘habit’. Asbestiform talc fibers are very long and thin.”(IARC 2010) The structure of platy talc is characterized by a hexagonal sheet arrangement of silicon-oxygen tetrahedral groups in a common plane which creates a double-sheeted structure. These sheets are easily separated which accounts for the “silky” or “smooth” feel of talcum powder products (IARC, 2010). As a mined mineral, the precise chemical and physical characteristics of talc are in part determined by the particular geological formations from which it is extracted. The local conditions can also produce “impurities” in the extracted talc including asbestos, quartz and various metals. It is claimed that cosmetic talcum powder products normally contain >98% talc (Zazenski *et al.*, 1995) but the purity may have been lower in the past. (IARC 2010) When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained in those products.

Asbestos is a commercial term that comprises six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite. Similarly to talc, these six minerals can occur in a non-asbestiform habit. Some types of asbestos are found in the same geological formations as talc.(IARC 2010)

By the 1970’s it was reported that asbestos fibers were found in commercial talcum powder (Cralley 1968; Rohl 1976), though there was some doubt expressed regarding the quantification of the exposure and the ability to discriminate between asbestiform and non-asbestiform talc. (Krause 1977; IARC 2010) The talc industry was constrained to remove asbestos from talcum powder products. Representatives of the industry have claimed that talcum powders were free of asbestos fibers since the 1980’s (Hopkins 2018; Pier 2018), but this assertion has increasingly come under doubt as number of labs have

reported finding asbestos fibers in talcum powder products. (Blount 1991; Paoletti 1984; Gordon 2014; Longo et al 2017; Longo et al 2018; Blount deposition 2018; Pier deposition 2018) These various studies that have reported finding asbestos in historic talcum powder samples have been challenged by other reports that failed to find meaningful amounts of asbestos in historic talcum powder samples. (CIR 2013; Anderson 2017) These various findings and opinions are somewhat complicated by the fact that both talc and asbestos have varied chemical and physical characteristics and various methods can be used to measure them.

What is clear is that asbestos, and all forms thereof, has been evaluated to be carcinogenic. It has long been recognized that inhalation of asbestos carries with it a risk of lung cancer and of mesothelioma, a cancer of the lining of the lungs, as well as larynx cancer. What has only recently been recognized is that women who are exposed to asbestos experience an excess risk of ovarian cancer. (Straif 2009; IARC 2012) This conclusion was based on five studies; a subsequent meta-analysis reported that the RR of ovarian cancer among asbestos-exposed women was a highly statistically significant 1.77 (1.37-2.28). (Camargo 2011) The route of exposure that generates risk of ovarian cancer among women exposed to asbestos is not clear, but inhalation and migration of asbestos particles to the ovaries has been proposed as a credible biologically plausible mechanism. (Miserocchi 2008)

Among the metals detected in talcum powder products are some which are recognized carcinogens, namely nickel and chromium. It is not known how widespread was the “contamination” of talcum powder products by these metals and how high were the concentrations in the entire commercial production of talcum powder products of the past several decades, and how these exposures measure up to exposures that may cause cancer. However, evidence that asbestos and some other known carcinogens have been detected in some commercial cosmetic talcum powder products and credible mechanisms that such particles can translocate to the ovaries is an important consideration in deriving an opinion on biological plausibility, and I will consider it below in my section on biological plausibility of a causal link between talcum powder products and ovarian cancer.

Alternative formulations of baby powder include cornstarch formulations, which have become available in the past 30 years. It was possible for women to purchase and use cornstarch products or talcum powder products. Most epidemiological studies have not tried to ascertain whether the women in their studies used talc-based or cornstarch-based formulations and many women may have been unaware of the composition of the powders they used at different times. It is impossible to ascertain with certainty from most of the publications whether the reported epidemiologic results pertain to talc-based powders or cornstarch-based powders or both. Those studies that did report results for cornstarch had few women self-reporting use of cornstarch and the risk estimates were rather imprecise and unstable. For those studies that did report separately the findings for talc-based and cornstarch-based formulations, I used the results for talc-based powders. For those that did not make such distinction, I used the results combining all types of powders as reported. If it turns out that there is an increased risk associated with talc but not with cornstarch, the inability to discriminate the two in statistical analyses would have the effect of diluting the estimates of risk due to talc. That is, the RR estimates would be attenuated.

5.3.3 Routes of exposure

Some studies reported results based on particular ways of using the powders, such as on feet or perineal use or use after bathing or use on sanitary napkins or use on diaphragms or use by male partners, and so on. And many studies just reported results for all routes of perineal exposure combined. For my Main analyses, I aimed to use the reported results pertaining to all types of perineal use combined. Where the results were reported for individual routes of exposure rather than all perineal use combined, I identified the one that came closest to powdering in the perineal area from all routes.

The number of studies providing results pertaining to any of those specific routes of exposure was much less than the number providing evidence for all routes combined and insufficient to provide reliable meta-analysis results for route-specific estimates of RR. Among the route-specific reports, the one that had most often reported RR results was exposure from dusting of sanitary napkins. I will conduct a separate meta-analysis regarding the risk of ovarian cancer in relation to use of powder on sanitary napkins.

5.3.4 Questionnaire items on use of talc powders

In the case of exposure to cosmetic talc powder, the most common and realistic way of ascertaining exposure has been to question women. But there are many ways this can be done, and indeed many types of questionnaires have been used. A very simple format that has been used is to ask a question such as “have you ever used powders in your genital area?” But, the validity of the response would be enhanced if the question is framed in a more specific manner, so long as the respondent can be expected to know the answer to the more specific question. One possibility would be: “have you ever used powders that contained talc on your genital area more than once a week for at least 6 months of your life? This would include powdering your genital area directly or powdering your underwear or powdering your diaphragm or powdering your sanitary napkin.” There are scores of ways such questions can be asked, and there has been variability in the methods of questioning among the different studies of powder use and ovarian cancer. In most studies, the questionnaire question about Ever Use was actually about Ever Regular Use, not Ever Occasional Use.

Among women who used powders, there can be an enormous range of usage from a few occasions in a lifetime to profuse daily usage. Among the many dimensions of talcum powder exposure that might influence the risk of cancer are the following: manner in which the talc was applied, age at which exposure began; if it ended, age at which it ended and years since it ended, frequency of use per day, week or per month, multiple applications including to genitals, undergarments, sanitary napkins, etc., and whether and how that varied at different ages. Some studies have used a single simple question, while others have used scores of questions to get at the lifetime history and many facets of powder use.

While I believe there are quality differences between the different studies in the way talc powder data have been collected, I have refrained from imposing my judgement about the quality of the questionnaire data on the selection of studies to include in meta-analyses.

5.3.5 Metrics of exposure

I used the reported results for the binary metric Ever Regular Use vs Never Regular Use, given the limitations of the available data, and using the investigators' decisions about how best to measure this. While this may seem like a simple tactic to implement, some studies were reported in such a way that in fact I had to make "judgement calls" about which of the reported results came closest to the desired metric.

For "dose-response" assessment, I used three pertinent metrics of exposure: duration (years), intensity/frequency (uses per day, week or per month), and cumulative number of applications, measured sometimes in absolute numbers or sometimes in quantiles. Of the three, the most meaningful is the cumulative number of applications.

6. My meta-analyses regarding talcum powder products and ovarian cancer: data included and results

6.1 Features of the studies

Following the exclusions indicated in Appendix Table A1, **Appendix Table A2** shows the studies that ended up being included in one or more of my meta-analyses, and brief descriptions of administrative and contextual features of each study. **Appendix Table A3** shows, for the same studies, some information about the talcum powder exposure variable and the covariates used by the authors in their control for confounding.

Appendix Table A2 shows that most studies were conducted in the USA. All but three were case-control studies and of the case-control studies, all but four used some type of population control series. Most studies had fieldwork data collection in the 1970's and 1980's; only a few studies started data collection after 2000. Table 3 shows for each study what exposure variable I was able to use to approach the notion of Ever exposed regularly to talc powder in the perineal region. Different studies had different questions in the questionnaire and different studies reported different variables. The questionnaires usually elicited lifetime use that was more than very sporadic, with terms like "regular" use. Only the Gonzalez 2016 study failed to ask about lifetime exposure before the interview; they asked about usage only in the preceding 12 months. The Gates 2010 study

asked about use of talc up to 1982 but not afterwards. Some studies asked separately about different routes of exposure and then rolled them together in statistical analyses, while some rolled all routes of exposure together in their questioning. The term that I show in Appendix Table A3 is the term that the authors reported in their publication of results; it is sometimes rather cryptic. Appendix Table A3 also shows which variables that the authors reported having used as adjustment variables. Sometimes these are variables that were explicitly included in final statistical models, and sometimes these were dealt with in a more indirect way such as a staged analysis in which a screening is conducted using a change-in-estimate procedure.

All meta-analyses were conducted using the well-known package Comprehensive Meta-Analysis Version 3. (Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013; <https://www.meta-analysis.com/index.php?cart=BFZW2135997>)

6.2 Association between binary variable talc powdering and all types of ovarian cancer combined – data and results

6.2.1 Individual studies and results on binary exposure variable

Table 2 shows RR results, as well as the corresponding 95% confidence intervals, for each informative study included in the Main meta-analysis or in any sensitivity analyses. (I will explain this distinction below.) As I explained in Section 4.1, the single number which reflects quite well the statistical strength of a study, be it case-control or cohort, is the number of exposed cases, and I have included this parameter in Table 2. Table 2 shows the RR reported in each study by Ever (regular) use of powder in the perineal region (all routes of perineal exposure including direct powdering on genital area, on sanitary napkins, on underwear and on diaphragms). The table shows results for all types of ovarian cancer combined.

Before conducting any meta-analyses, we can peruse the results in Table 2 to observe certain patterns.

Of the 33 RR results shown in Table 2, two are below 1.0, one equals 1.0, and 30 are greater than 1.0. On the null hypothesis that there is no true association between powdering with

talc and ovarian cancer, we would expect as many of the RR estimates to be above 1.0 as to be below 1.0. The observed distribution (2 below and 30 above) is clearly and strongly in defiance of the null hypothesis. Further if we rank the RR estimates from lowest to highest, the median value, the one in the middle, would be 1.34.

This informal analysis does not take into account that the 33 estimates in Table 2 are not strictly independent of each other. There are various ways to carve out independent sets of results from this list of results in Table 2, and the meta-analyses will be designed to do that. But no matter how the studies are configured, it will be found that one or two of the RR estimates are below 1.0 and somewhere between 20 and 26 are above 1.0. Such an imbalance cannot be due to chance.

6.2.2 Strategy for Main analysis and sensitivity analyses

An investigator typically has in mind a strategy for analysing and presenting the results. There may be some judgement or assumptions involved in deciding on the strategy. The investigator may wish to see how the results would be affected if other judgements or assumptions were made. In other words, how robust are the results to alternative judgements and assumptions. Such alternative analyses are referred to as *sensitivity analyses*.

There were several dilemmas in selection of studies and results to include in the meta-analysis. I made decisions in each case that I believe provides the best basis for a meta-analysis. But in deference to other possible decisions that might have been made, I conducted some sensitivity analyses as well. I list what the dilemmas were and which options were selected for Main analyses and for sensitivity analyses.

a. Terry 2013 and Wu 2015. The Terry 2013 paper brought together data from 8 different research teams. Some of those teams had previously published their results on talc and ovarian cancer and some had not. Normally, a pooled analysis would take precedence over the individual component studies. In this case, however, there were complicating factors. The Los Angeles component study of Terry 2013 (Wu, Pike and colleagues) was conducted in stages and the Terry 2013 pooled analysis only had access to the early stage. Subsequently, Wu and colleagues carried on with their data collection, and published a

more complete set of results from their study in Wu 2015. The Terry 2013 paper contained 208 exposed cases from the Los Angeles study, whereas the Wu 2015 paper contained 701 exposed cases. In the entire Terry 2013 paper there were 2600 exposed cases. Ideally, we would wish to exclude from the 2600 exposed cases in the Terry 2013 paper, the 208 exposed cases that came from the early Los Angeles data. But that information was not available. Thus there is an 8% overlap between the exposed cases in the Terry 2013 paper and those in the Wu 2015 paper.

I adopted the following strategy. For the Main analysis, I included both Terry 2013 and Wu 2015. The 8% overlap of exposed cases is unfortunate but I believe its impact would be trivial, and in any case we will have some empirical evidence of its impact from a sensitivity analysis.

I conducted sensitivity analyses using a different strategy. The Terry 2013 paper contained a table in which the individual results of the 8 component studies were reported. I used the results as reported there for 6 of the 8 component studies, for which the Terry paper contained the latest results. For the Los Angeles study I used the result reported in Wu 2015 which was much more complete than the L.A. study result in Terry 2013. The eighth study was the study of Cramer that was one of the components of Terry 2013 but that was also reported subsequently in Cramer 2016. It is not clear whether the Cramer 2016 paper contains more up to date data than the corresponding component in Terry 2013, but it possibly does.

To summarize, the Main analysis contained pooled result from Terry 2013 and the result from Wu 2015. There were sensitivity analyses that dropped the pooled result from Terry 2013, but included the (apparent) latest published result for each of the 8 components.

b. Nurses Health Study. This cohort study was initiated in 1976 and was not a study of talcum powder products and ovarian cancer. The study involved a wide-ranging annual questionnaire which inquired about many health related issues. In 1982 there was a very succinct question about use of body powders. The cohort has been followed-up to ascertain the occurrence of cancers (or other diseases). There was a publication that contained results on talc and ovarian cancer from this study in 2000 (Gertig 2000); later, after more

years of follow-up there were two further papers presenting results on talc and ovarian cancer (Gates 2008 and Gates 2010). Clearly the Gertig result did not belong in my meta-analysis, since it was subsumed by subsequent analyses, but the choice between the Gates 2008 and Gates 2010 was not so obvious. Gates 2008 was based on a nested analysis of a subset of the cohort that probably entailed better control for confounding. Gates 2010 was based on the entire cohort and thus on a much larger sample size. The two RR estimates from the Gates papers are quite different from one another (RR=1.24 in Gates 2008 and RR=1.06 in Gates 2010). It is not clear whether the difference in results is due to the different design and analytic procedures used in the two papers. The authors did not comment on the inconsistent results.

My Main analysis included Gates 2010 but not Gates 2008. Some sensitivity analyses contained Gates 2008, but not Gates 2010.

It should be noted that whereas I did not use the Gertig paper results in the meta-analysis of Ever / Never Use of talcum powder products, I did use some dose-response results from Gertig because subsequent publications from the Nurses' Health Study did not present such results.

c. Schildkraut (2016). This was a case-control study of ovarian cancer among African American women. The fieldwork and interviewing was carried out from 2010 to 2015. The authors speculated that publicity surrounding two class action lawsuits on talc and ovarian cancer in 2014 may have subsequently induced bias in the validity of reporting of talc exposure. Consequently, in their analysis and report, they presented two sets of results, one for all women in the study, and another for those interviewed before 2014. It is impossible for me to evaluate the validity of the speculation, as it was for the authors. Consequently I will use the results from the entire sample and those from the pre-2014 sample. I refer to the entire Schildkraut study result as Schildkraut A and the pre-publicity result as Schildkraut B.

The Main analysis contained Schildkraut A. Some sensitivity analyses contained Schildkraut B.

d. Shushan (1996). This ovarian cancer case-control study, conducted in Israel, reported results on talc and ovarian cancer, but the report was quite cryptic regarding the data collection and the talc exposure variable.

The Main analysis excluded Shushan 1996. Some sensitivity analyses included Shushan 1996.

6.2.3 Results of meta-analyses on binary exposure variable for all ovarian cancers

Figure 1 shows the printout from the Comprehensive Meta-analysis (CMA) package for the Main meta-analysis for the association between ever regular use of talc powder in the genital area and all types of ovarian cancer combined. 21 RR results were used in the Main meta-analysis, but the Terry 2013 study represents 8 different study teams and 10 distinct studies. In the forest plot, I have ordered the studies in increasing magnitude of the RR estimate. It can be seen that only one study produced an RR estimate to the left of the null value of 1.0, while 19 studies produced an RR estimate to the right of the null value of 1.0.

The meta-estimate of RR is 1.28 with a 95% confidence limit from 1.19 to 1.38. The p-value is too small to register in 2 digits. This is a very highly statistically significant result. The probability of this result being attributable to chance is vanishingly small.

The 21 RR estimates in this Main meta-analysis had a fairly low p-value for heterogeneity, 0.07, but it was not statistically significant. This means that there was considerable variation in RR results across the studies, but this might have been due to chance. That there is significant variation in RR estimates is not surprising. The different studies were conducted among different populations, using different methodologies. It would be surprising if there was no variation. It is nevertheless true that in the current state of knowledge the best estimate of RR is the meta-estimate of 1.28.

Table 3 shows the results of the Main meta-analysis again and contrasts it with the results of seven sensitivity analyses that embody alternative plausible strategies for selecting studies and selecting results within studies. These alternative strategies had almost no effect. The meta-estimates of RR varied in a narrow range from 1.26 to 1.30. Even the lowest of these would lead to the conclusion that there is a highly significant association.

It can be affirmed, quite confidently, that the apparent overall elevated risk for women who had ever used such powders is not an artefact of chance variation. This conclusion is not new. It has been stated by the authors of previous meta-analyses. However, I believe this conclusion is based on the most current and reliable data now available.

From a statistical point of view, each of the studies listed in Table 2, except for one or two outliers, shows a 95% confidence interval that overlaps substantially with the confidence interval of the meta-RR estimate (1.19 – 1.38). Further, the majority of the study-specific confidence intervals (including 2 of the 3 cohort studies) include the overall meta RR of 1.28. This shows that there are few if any studies that are not compatible with the overall RR estimate.

6.2.4 Other contemporaneous meta-analyses on binary exposure variable for all ovarian cancers

I started to conduct my meta-analyses in 2015 and revised it in 2018. Towards the end of my analyses, I discovered that two other teams of researchers were carrying out meta-analyses on the same topic at almost the same time. The simultaneous and independent conduct of these three meta-analyses provides a unique opportunity to cross-validate the methodologies and results. (I knew nothing about the two others and I assume they did not know either about mine or the other meta-analysis.) It is sometimes portrayed that meta-analysis is a fairly automated procedure which should produce identical results irrespective of who carries it out. This is far from true.

Even before the statistical part of the meta-analysis is conducted, the author of a meta-analysis has to assemble all of the relevant data. That usually consists of two steps: identifying all informative studies on the topic and identifying the relevant result from each study to include in the meta-analysis. There are many ways to do these steps, and it is not surprising that different, equally competent, investigators may make different decisions about how to identify the studies and how to identify the most relevant results. This is particularly true in the area of observational epidemiology research, as opposed to clinical trials research. Research designs and methods of conduct and reporting are much more standardized in clinical trials research than they are in observational epidemiology. In the

area of research on talc and ovarian cancer (which is observational) there are many opportunities for judgement of the author of the meta-analysis to come into play, and in section 5.3.1 I have listed some of the decisions that I made, in the way I managed the selection of studies.

The two other meta-analyses were conducted by Berge et al (2018) and by Penninkilampi et al (2018). They conducted rather different search procedures than I did. Since I had already participated in the IARC review and the Langseth 2008 paper, I already had a head start on collecting the relevant scientific literature. **Appendix B** shows a 3-way comparison of the studies that were included in the meta-analyses by the three authors, and the data from each study that were judged to be most relevant by each author.

As a generalization, it can be seen that the three synchronous meta-analyses identified more or less the same studies and that in general they extracted the same result from each study; but this was not always the case. For my own meta-analysis, I was comforted to note that there was no study that was identified by one of the other meta-analyses that I had missed in my search of the literature (Appendix Table A1).

One of the main points of discordance in procedure was how the three analyses dealt with the Terry 2013 study. Namely, in my Main analysis I used the result of the pooled Ever/Never RR that was quoted by the Terry study, and dropped from consideration the various component studies of the Terry analysis. By contrast, the two others (Berge and Penninkilampi) adopted the strategy of using the results of the individual component studies rather than the overall pooled result. Berge 2018 used the results of the individual component studies as reported by Terry 2013, for most component studies, but for two component studies they used results that were reported in publications that gave results with additional cases. Penninkilampi 2018 also used individual component study results rather than the Terry 2013 pooled result. There are trade-offs between these different approaches. I prefer to use the Terry 2013 pooled result for two reasons. First, a pooled analysis with a standard set of covariates and a standard statistical model is considered superior to a meta-analysis of the components study results. Second, each publication tends to show a variety of results, and the author of the meta-analysis has to choose a

“best” one to represent the “bottom line” from each study. In the Terry pooled analysis, it was the investigators of the original studies, who were also co-authors of the pooled analysis, who chose which would be the “best” result to represent the study, and this in my opinion is more reliable than outside authors making that decision.

Table 4 shows the meta-RR results from each of the three meta-analyses. Notwithstanding the differences in choices and strategies of the three meta-analyses, the meta-RR results are quite similar, ranging from 1.22 (1.13 – 1.30) in the Berge analysis, to 1.28 (1.19 – 1.38) in my analysis, to 1.31 (1.24-1.39) in the Penninkilampi analysis. These three sets of results are really quite close to each other.

The methodology I used is sound and reliable and consistent with the high standards of my discipline. The strategy and decisions I made in relation to the studies selected and the data abstracted from each informative study is consistent with that methodology I use in my professional practice, and that has earned me recognitions and honors throughout the world.

The results shown in Table 4, are in the same “ballpark” as the meta-analysis previously conducted by Langseth 2008 and they are based on a larger pool of accumulated publications. This indicates that recent evidence is consistent with older evidence and reinforces the consistency of the evidence.

6.2.5 Meta-analysis on powdering of sanitary napkins

Tables 2-4 pertain to RRs for the combination of all routes of exposure to the perineum, including direct dusting and dusting on sanitary napkins, diaphragms, underwear, and condoms. When such an exposure variable was not provided in the paper, I used the one that came closest, with priority to dusting on the body directly. Most studies did not report RR results for every route of exposure separately. For the studies that did so, the numbers exposed were much lower than for all routes combined and there was limited statistical power in those analyses. Of the different routes, the dusting on sanitary napkins was generally the most commonly reported route apart from direct dusting. Consequently I assembled the data pertaining to dusting on sanitary napkins and conducted a meta-analysis of those results.

Table 5 shows both the individual studies that had results on sanitary napkin dusting and the meta-analysis result for those studies. The meta-RR was 1.08 (95%CI 0.89 - 1.31), heterogeneity $p=0.09$. Given the overlap between the confidence intervals between this meta-RR estimate for sanitary napkin powdering and the meta-RR for powdering the perineal area via any route (1.28; 95%CI 1.19 - 1.38), it cannot be affirmed that the result for sanitary napkins is statistically significantly lower than the meta-RR results in Table 3 for all routes of exposure; but the tendency is in that direction.

Berge 2018 and Penninkilampi 2018 also meta-analysed the data on use of powder on sanitary napkins. By contrast with my results, Berge 2018 reported an RR of 1.00 (95% CI 0.84-1.16) and Penninkilampi 2018 reported an RR of 1.15 (95% CI 0.94-1.41). Since their publications do not make it clear which studies and which results were used in these analyses, I cannot see easily what explains the discordance among the three meta-analyses for sanitary napkins powdering. In any case, it certainly appears that the RR was lower for application to sanitary napkins than it was for general perineal application. The interpretation of this finding is not self-evident. The different routes of exposure may entail very different frequency of exposure. For instance, whereas use of powders on sanitary napkins might involve exposure on only a few days per month, regular use on the perineal region often involves daily or near daily application. I am unaware of any evidence that would address the question of whether regular use on sanitary napkins leads to greater or lesser delivery of talc particles to the portal to the ovary than does regular powdering on the perineal region.

In any case, irrespective of the evidence regarding sanitary napkin exposure, the results in Tables 2 and 3 clearly show an association between exposure to talc in the perineal region and risk of ovarian cancer.

6.3 Dose-response – cumulative exposure, duration and frequency

An important part of the evaluation of causality is to determine whether the results display any kind of dose-response pattern. Tables 6 to 8 show results for various quantitative metrics of exposure.

Trends by cumulative exposure: **Table 6** shows results from five publications that presented results based on a cumulative amount metric. Four of the studies were based on counts of numbers of powderings, while the Cook 1997 result was based on counts of the number of days on which powdering occurred. As can be seen by perusing the column of numbers of exposed cases, the Terry 2013 results dwarf the others in terms of the statistical information they contain. The Schildkraut study, with about one-tenth as many subjects as the Terry study, nevertheless has as many subjects as the other three studies combined. The relative statistical power of the different studies is also manifested in the width of the confidence intervals.

The evaluation of the statistical significance of a trend is not a methodologically straightforward endeavour. Of particular concern is the question of whether or not the test for trend among subjects in different “dose” categories should include or exclude the unexposed category. My view is that it depends on whether or not the study results for Ever/Never exposure are part of the buffet of results presented by the authors. Namely, if the only result presented is a dose-response analysis, then it is appropriate to include the unexposed category as part of the study results. If the Ever/Never result is presented and then a dose-response analysis is conducted, it is preferable to maintain statistical independence of the two analyses by excluding the baseline unexposed category from the dose-response analyses. I will interpret the data from these studies in light of this interpretation of trend tests.

The three smallest studies in Table 6 show no evidence of a dose-response pattern. However, the estimates are so imprecise, as evidenced by the very wide confidence intervals, that they are virtually uninformative regarding the presence or the absence of dose-response.

When looking at the Terry 2013 results, which assemble data from eight teams and 10 studies, the confidence limits are much tighter and the estimates of RR much more precise. The p-value for trend (excluding the unexposed group) is 0.17. Nevertheless, with a reference value of RR=1.0 among unexposed, and with point estimates of RR in four quartiles of cumulative exposure of 1.14, 1.23, 1.22, and 1.32, these results are certainly

compatible with the presence of an underlying dose-response relationship. Note that the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response. Similarly, the Schildkraut 2016 study results, while based on only two lifetime cumulative “dose” categories with point estimates of 1.16 and 1.67, are also compatible with a dose-response pattern.

Trends by duration of exposure: **Table 7** shows the results of those studies that presented RRs by duration of use. The Terry 2013 pooled analysis did not report results by duration of use; however, some of its constituent studies did so and are included here. The numbers in each of the duration categories in each of these studies is quite small, and consequently the RR estimates are very imprecise, with wide confidence intervals. The categorisation of duration differed quite a bit among the studies and it is not easy to compare results between studies. There is no indication of a dose-response relationship in these results. Though, the wide confidence intervals make it impossible to affirm that there is evidence against dose-response. Further, the largest study showing results by duration of use, Wu 2015, did find a significant increase in risk with increasing duration.

Trends by intensity of exposure: **Table 8** shows results of those studies that reported by intensity (i.e. frequency) of usage. This ignores duration of usage. Like the results in Table 7, the results in individual studies are based on rather small numbers and they entail imprecise estimates of RR. Also like Table 7, the pattern of results is equivocal. There is no clear evidence for or against an underlying dose-response.

The Berge 2018 paper also looked at dose-response. They only looked at trends by duration of usage and frequency of usage, analogous to my Tables 7 and 8. However they actually fitted continuous variable models and found that there were significant trends in risk by duration and by frequency of exposure. They did not examine trends by cumulative exposure, and in particular they did not use the results from the Terry 2013 pooled analysis, which in my view is the most informative evidence available on dose-response.

Penninkilampi 2018 looked at risk according to long duration of usage and found no trend. They also looked at cumulative exposure with total number of applications, and they reported a slightly higher RR for women with greater than 3600 applications (RR=1.42)

compared with women who had fewer than 3600 applications (RR=1.32). I cannot determine from the paper which studies were included in this analysis and in particular whether the pooled Terry 2013 dataset was included. While the Terry 2013 and Penninkilampi 2018 papers both contained some results on dose-response, they are not included in Tables 6-8 because they are not original data collection studies; like mine, their's is a review of other studies which are contained in Tables 6-8. As indicated above, all other things being equal, the best metric of the three quantitative ones is the cumulative exposure metric, and that is the one that happens to provide the most statistically reliable data. Thus, the evidence from Table 6 overrides the weaker evidence from Tables 7 and 8. The evidence from the Terry 2013 paper is the most important piece of evidence we have on dose-response. The evidence from the Terry 2013 paper is compatible with the presence of a dose-response relationship between use of powder and ovarian cancer.

6.4 Subtypes of ovarian cancer - in particular, serous invasive tumors

Most studies that provide results on RR between talc powder and ovarian cancer provide results for all types of ovarian cancer combined. Less than half of the published studies have also provided results of the associations between talc powder exposure and various subtypes of ovarian cancer.

To the extent that talc exposure might have different effects on different subtypes of ovarian cancer, there would be a clear advantage to segregating the evidence by type of ovarian cancer and evaluating the evidence for each subtype. The serous-invasive subgroup comprises over half of all cases, and the rest are split among several other histology-behaviour subgroups (mucinous, endometrioid, clear cell, others, and these can be further subdivided by invasive or borderline). Those latter subgroups entail very small numbers each and barely provide enough data, in most studies, to produce informative risk estimates. In those studies, where results were presented by histologic-behaviour subgroups, it is my judgement that there is no strong consistent pattern indicating that one subtype has higher risk than another. Of course, there is variability in point estimates of RR, but on the one hand the variability in RR estimates between ovarian cancer subtypes within studies is not greater than would be expected from chance variability (mostly, the

confidence limits overlap considerably), and on the other hand, from study to study, it is not always the same subtype that seems to have the highest or lowest relative risks.

In the largest assembly of cases subdivided by histologic subtype, the Terry 2013 pooled analysis, the results by subtype were as follows:

- Serous: n=1197; RR=1.24(1.13-1.35)
- mucinous: n=94; RR=1.06 (0.82-1.36)
- endometrioid: n=304; RR=1.20 (1.03-1.40)
- clear cell: n=187; RR=1.26 (1.04-1.52).

Other than serous invasive tumors, there is no other subtype for which there are sufficient numbers of studies and sufficiently precise estimates of RR in each study to provide reliable estimates of the overall RR. While the results for endometrioid and clear cell tumors show risks that are closely aligned with those for serous tumors, the result for mucinous tumors are so imprecise, because of the very small numbers of such tumors, that the estimated RR of 1.06 is very unreliable.

Consequently, and because there were multiple studies apart from Terry 2013 that presented results for serous tumors, I decided to conduct a meta-analysis for serous/invasive ovarian cancers, but not for other subgroups. The meta-analysis on serous invasive tumors will indirectly inform us also about the relative risks for other types of ovarian cancer. Namely, if the RR for serous invasive tumors is similar to that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) will not be very different from the overall RR. If the RR for serous invasive tumors is much greater than that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) are lower than the overall RR. Similarly, if the RR for serous invasive tumors is much lower than that for all ovarian tumors, it will

imply that the risks for other types (the complement of serous invasive tumors) are higher than that for all ovarian cancer.

Table 9 shows all the studies that reported results concerning the link between talc exposure and serous/invasive tumors. There were 8 informative studies, including Terry 2013, which carried by far the most statistical weight. The meta-RR estimate for serous/invasive tumours was 1.25 (1.1.15- 1.36). This is very similar to meta-RR for all ovarian tumors, albeit based on a smaller number of informative studies. Thus there is no persuasive evidence in these studies, taken as a whole that the effect of talc differs by histologic subtype of epithelial ovarian cancer. That is, with such a tiny difference in RRs between that for all ovarian cancers combined and that for serous invasive ovarian cancers, it can be safely inferred that the RR for other types of ovarian cancer (the complement of serous invasive) would not be far from the overall RR of 1.28.

6.5 Conclusion from meta-analyses and dose-response considerations

My opinion, based on up-to-date data and meta-analyses, is that the RR between ever perineal use of talcum powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). This result is highly statistically significant.

We can rule out random variability as a possible explanation for the apparent excess risks. Further, the examination of results according to the “amount” of exposure, and notably the cumulative exposure variable used by Terry 2013, shows that the higher the exposure, the higher the risk.

Such a pattern of findings can have only two possible explanations: it must be the result of some sort of bias or confounder that operated in multiple studies or it must be the result of a real causal association.

7. Misconceptions and possible biases

In reaching my opinions, I have objectively looked at the data and scientific literature and considered the points of view of others who do not share the conclusions I have reached. There are generally two sources of disagreement: misconceptions of epidemiologic or

statistical concepts which I address below in Section 7.1 and professional judgement of the likelihood of errors and biases in the various epidemiological studies, which I address in Section 7.2.

7.1 Some prominent misconceptions in reviewing the evidence

Table 10 lists some prominent misconceptions, and I will address them here.

Misconception: "Cohort studies are more valid and informative than case-control studies."

As can be seen in Table 2, the case-control studies tended to produce higher RR estimates than the cohort studies. It has sometimes been claimed that cohort studies are more valid than case-control studies. There is no theoretical or practical reason why such a blanket assertion should be universally true. There are many factors that influence the validity of a particular result in a particular study and it cannot be reduced to any simplistic assertion that cohort studies are more valid than case-control studies, or vice versa. In the next section, I will go through a number of potential sources of distortion of results from epidemiologic studies, and I showed that some of them might occur in cohort studies, some in case-control studies, and some in both. Some of these distortions very likely occurred in some or all of these studies that provide data on talc and ovarian cancer. On balance, I believe the results of each of these case-control studies concerning female use of powders and ovarian cancer are credible, and perhaps more so (for reasons given in section 7.2), than the analogous results of each of these cohort studies.

Misconception: "Hospital-based case-control studies are more valid and informative than population-based case-control studies."

In a case-control study, the design objective is to define a study base, or a population base, in which the cases might occur, and to identify representative samples of cases and of controls in that study base. The purpose of a control group is to provide an estimate of the prevalence of exposure to the factor under study in the base population that gave rise to the cases. In many instances, the best source of controls for case-control studies is a population list of some sort. But sometimes using a population list is not feasible or

desirable, and an alternative can be to select controls from among hospital patients with conditions other than ovarian cancer. This was done in some of the ovarian cancer case-control studies.

The most common generalization made by epidemiologists is that population-based case-control studies are more valid than hospital-based case-control studies. In fact, neither this nor the opposite statement that I articulated as a Misconception, is universally correct. Validity of a case-control study depends on the specific design features and circumstances of the study.

It is possible that some types of hospital controls have patterns of usage of powders that are different from those of women in the general population, either because the powders are actually causally associated with the diseases that those women have or because their disease or condition that led them to be hospitalised induces some women to take up the use of such powders. If such a mechanism was present in a hospital-based case-control study, it would likely lead to an artificially attenuated RR, not an artificially inflated RR.

Misconception: "Counting the number of statistically significant results is a valid way of assessing consistency of results among multiple studies."

This misconception betrays a lack of understanding of statistical significance. As can be seen in Table 2, several of the individual studies listed in my meta-analysis did not find a statistically significant increase in RR. This has been cited by some as evidence that there is no real causal link.

In fact, meta-analysis is a method that was developed precisely because counting significant results is an invalid way of synthesising knowledge. Namely, a result from a single study may fail to achieve statistical significance either because there is no risk in that study, or because the statistical power of the study was limited. Meta-analysis was developed in order to combine evidence from multiple studies that may be under-powered on their own, but when combined show an effect that might be statistically significant. The meta-analysis cannot conjure a statistically significant meta-RR if the individual study RRs do not systematically lean in the direction of an excess risk, and they do so in the area of talc and ovarian cancer to a degree that cannot be explained by random fluctuation.

Misconception: "You cannot prove causality with an RR less than 2.0."

There is nothing in epidemiologic theory or practice that justifies such a statement. Indeed, this assertion about an $RR \geq 2.0$ threshold does not exist in epidemiology. There are many well-established causal relations where the RR is less than 2.0. Table 11 lists a number of such examples. In clinical medicine also, it is very common to strive to find therapies that reduce the risk of death from some disease by as little as 10%, and several such discoveries are well documented and have been integrated in medical practice, even though the change in risk is small.

Misconception: "If a product has been used for a long time it must be safe."

It has been argued that since talc powder has been used for many decades by millions of women (and men and children), it has stood the test of time and should be considered safe. This is a specious argument.

Most agents in our environment or in our lifestyle which are now considered dangerous were used for decades or centuries without falling under a cloud of suspicion. These include such factors as cigarette smoking (many cancers and cardiovascular disease), asbestos (lung cancer), sunlight (skin cancer), ingesting very hot liquids (esophageal cancer), and many others.

Misconception: "Government agencies provide the most reliable and authoritative statements regarding the lack of carcinogenicity of talc."

Various national and international agencies have websites which list carcinogens. Examples are: National Cancer Institute (NCI), National Toxicology Program Report on Carcinogens (NTP-RoC), International Agency for Research on Cancer (IARC). It can be argued that these agencies, which undoubtedly have scientific credibility, would not put on their websites information that is out of date or invalid. However, that claim is false.

IARC has a rigorous evaluation process which is considered quite authoritative throughout the world, including in the U.S. But the evaluation is carried out at a certain point in time. The last time talc was evaluated by IARC was in 2006. Based on the evidence available then, the panel rated talc as a "possible" carcinogen. Additional evidence has been accumulated

and come to light since then, but there has not been a new evaluation by IARC. (There are potentially thousands of agents to evaluate, and IARC has resources to only evaluate a few each year. Thus they cannot keep re-evaluating the same ones as soon as new evidence is published.)

NTP-RoC is a congressionally-mandated program whereby the agency is obligated to periodically publish lists of known and suspected carcinogens. Unlike IARC, it appears that the people who make the decisions are internal RoC scientists, rather than external experts, with advice from outside experts. Also unlike IARC, the biennial reports only contain listings of those agents that have been deemed to be definite or likely carcinogens, so there does not seem to be a statutory listing of all agents that have been considered. From the minutes of a meeting of the Board of Scientific Counsellors of NTP held in 2000, it appears that the issue was deferred. I am not aware that the RoC has conducted a subsequent review of talc; although, when renominated in 2004, NTP deferred to IARC.

NCI provides a website for doctors where they indicate for each type of cancer, what are the known risk factors. Based upon my understanding, they do not carry out a rigorous evaluation along the lines of the IARC evaluations or even the NTP evaluations. It is a rather superficial process compared with the IARC process and it depends on the existing knowledge of the committee members which in a short time opines about possible associations between each of the scores of cancer types and scores of potential risk factors. This is not to argue that the members of these committees are less expert than the members of the IARC committees, but the NCI committee members have a short time (apart from their main jobs) to review hundreds of possible factor-cancer associations, whereas the IARC committee members have weeks to review just a few.

Scientists and public health agencies regularly consult the IARC evaluations and those of the NTP. The NCI website for doctors is not considered an up-to-date and cutting edge source of information. This is, of course, no reflection on the gravitas of the NCI as a whole, which has much more invested in its original research mission than in its website for doctors.

There are other organizations which may put some information about causes of cancer on their websites. Importantly, I have not seen any agency or organization, including the FDA, that conducted a rigorous evaluation of the epidemiologic and non-epidemiologic studies like we did at IARC in 2006.

Misconception: "A biological mechanism must be proven before we can establish causality"

There are innumerable examples in medical history of discoveries of risk factors or treatments that did not require knowledge of the mechanisms of pathogenesis in order to determine causality. I have compiled a few such examples from medical history and show them in **Appendix C**.

Very often, the initial suggestion was met with scepticism from the vantage point of biologic plausibility. In fact, very seldom have the essential features of biologic plausibility been worked out by the time the epidemiology has convincingly demonstrated that the association is causal. This can be asserted for the early discoveries such as the cancer causing effects of certain chemicals in dye production facilities, certain metals in various heavy industry facilities, certain emissions of combustion of fossil fuels, ionising radiation, and even cigarette smoking. In most of these examples, it was decades after the epidemiologic evidence became convincing that credible mechanistic theories were proven; though, for some, the biologic mechanisms remain unknown.

Indeed in the guidelines of the IARC Monographs, it is stated that if there is "sufficient" evidence of a risk of cancer from epidemiologic studies, then irrespective of the evidence from animal experimentation and other biologic evidence, the agent in question should be considered a Group 1 carcinogenic agent. My point here is that the demonstration of a proven biologic mechanism is not a prerequisite for demonstrating that an agent is a human carcinogen. Reliable empirical epidemiologic evidence of an association is a sufficient basis for demonstrating causality; the presence of a credible biologic mechanism enhances the degree of proof, though that often lags decades behind the general recognition of causality, as exemplified by the examples in Appendix C.

It is not my opinion that we should ignore or set aside consideration of biologic plausibility. As Hill (1965) indicated in outlining the thought process for establishing causality, biologic plausibility is one of the dimensions to be considered. But, he also cautioned that, “this is a feature I am convinced we cannot demand”. Thus, as I have done in other contexts in regard to other putative carcinogens, I am able to draw causal inferences about talc irrespective of whether a causal mechanism has been proven.

Misconception: “Bradford Hill criteria comprise a checklist of necessary conditions”

As I explained in section 4.2, the “aspects” that Hill listed are not “criteria” and they are not necessary. This point has been made and is widely accepted by epidemiologists. The list of “aspects” in Hill’s original paper have been rephrased and reworked in many textbooks and by most agencies that refer to them. They provide a framework and not a checklist.

7.2 Alternative explanations - Biases and errors

Before inferring that the strong statistical evidence that use of powder in the perineal area by women is associated with ovarian cancer may represent a causal relationship, I considered alternative explanations for these observations. In this section I will consider a number of potential sources of distortion of the risk estimates, under various rubrics. Some of the potential sources of distortion are unique to cohort studies, some are unique to case-control studies, and some can affect both types.

7.2.1 Bias due to non-response or non-participation

This is a potential source of bias in case-control studies.

Among all potential cases and controls who meet the study’s eligibility criteria, some participate and some don’t. The most common reasons for non-participation are: refusal; inability of the researchers to contact the person because they moved or are too sick or died or are otherwise unavailable; if access to the subject is via the treating physician or medical staff, there could be obstacles at that level. If the factor under study, hygiene powder use, is correlated with the likelihood of participation and if the participation rate is low, this could lead to biased estimates of RR. Such bias could artificially inflate or deflate the RR depending on how the various variables are related to each other. If response rates

are low, say below 70%, and differential both by case-control status and by exposed – non-exposed status, this could lead to biased RR estimates. For such a bias to explain the outcomes seen, it would require quite strong associations between likelihood of participation and powder use, and quite strong differences in such associations between cases and controls. In my opinion, it is very unlikely in the context of these studies that response rate differentials would be great enough to induce such large bias.

7.2.2 Recall or reporting bias

This is a potential source of bias in case-control studies.

Because the exposure history is collected retrospectively, it is subject to both non-differential recall errors (see below), and to recall or reporting bias between cases and controls. Cases and controls may have different motivation and proclivities to recall and report use of powders. If it were true that cases had a greater tendency to over-report powdering history or if controls had a greater tendency to under-report powdering, then this would lead to an artefactual exaggeration of the RR.

There are a few possible causes of such differential reporting. First, it might be hypothesized that there is a general tendency for cases in case-control studies to acknowledge behaviours or exposures with much greater frequency than controls just because they are more invested in the research than are controls. They may wrack their brains during the interview to find instances of the queried behaviour or exposure that controls don't pay much attention to during the interview, because the controls just "want to get the interview over with". If this were the case, we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies. But in my experience, this does not occur. (I have conducted many case-control studies, each study eliciting information on many lifestyle factors and exposures. It has not been the case that cases systematically report more exposures than controls.) Furthermore, and more pointedly, if such a phenomenon were operative in these case-control studies of ovarian cancer, we would see elevated RRs when women were questioned about the use of powders on other parts of their bodies than the perineal area. In fact, several studies did ask such questions. In the Terry 2013 analyses, based on very large numbers of women, the

overall RR for ever use of hygiene powder on non-genital areas of the body was 0.98 (0.89-1.07), in stark contrast to the analogous result for genital use of 1.24 (1.16-1.33). In other words, when questioned about powdering in non-genital areas, controls were as likely to say “yes” as cases. Clearly there was no tendency for cases to indiscriminately report exposures more frequently than controls.

A second possible reason for such a situation to arise is if there was widespread knowledge about powdering being under suspicion for ovarian cancer. In such a situation women who have heard about this might internalize the notion that powdering may have caused their cancer, and they might ruminate with such intensity on the notion that they might imagine that they had used powders at some point in the past. But for most of the period of data collection in these studies, there was very little public discussion of a possible linkage between powdering and ovarian cancer and I doubt if more than a handful of the thousands of women interviewed in these studies would have heard of such a hypothesis before being interviewed.

In my opinion recall bias is not likely to have produced the kinds of RRs we see in these studies.

7.2.3 Non-differential (or random) error in recall or reporting of exposure to powders

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

Reporting past history of activities and exposures is always subject to some degree of error; it can result from ambiguity or misunderstanding of the questions, failures of memory, or inattention. And this is certainly true for history of powdering. If such error is non-differential (i.e. equally present for cases and controls in the case-control context) it has an effect on RR estimates that is rather predictable. Namely, as I explained above, it has the effect of artifactually decreasing the RR. The degree of attenuation is roughly proportional to the degree of error or misclassification. If there really is a causal association between powdering and ovarian cancer, then we can be rather certain that the true RR is higher than what we can see in the various studies that have reported RRs.

Furthermore, we might make some reasonable inferences about the impact of reporting error on dose-response trends as well as on the overall RR. It is reasonable to surmise that the amount of reporting error is quite a bit higher for the details of past usage (duration of usage, intensity and frequency of past usage) than it is for the simple fact of usage. That is, there is less error in a woman's report of whether or not she ever used powders on a regular basis than in her report of the details of the usage, even if powdering behaviour may be a relatively stable habit. The consequence of this is that the RR based on ever/never usage (Table 2) is less subject to artefactual attenuation than the RRs based on categorizing the duration or intensity or cumulative amount of usage (Tables 6-8). This is a possible explanation of why there has been a much clearer signal of elevated RR for ever/never usage than there has been for dose-response.

There is likely to be more measurement error of exposure to powders in cohort studies than in case-control studies, for several reasons. First, because the cohort study questionnaires attempted to broach topics that could be relevant to many types of cancer and indeed many diseases, the questions posed in the cohort study questionnaires about talc powder use tended to be much briefer and probably less effective at eliciting valid information than the questionnaires used in case-control studies of ovarian cancer. For instance, the cohort studies did not elicit information on timing or duration of past usage, and one of the cohort studies did not even attempt to elicit information about use of talcum powder products over 12 months before the interview. Second, whereas a case-control design involves a woman looking backwards over her life from the time of incident cancer onset and thereby addressing the entire relevant period of potential exposure, the woman in a cohort study reports on her past usage as of a certain point in her life, but there may be 10-20 years subsequent in which her habits could have changed, and of which the cohort study has no knowledge. The women in the cohort studies were "locked into" their exposure category at baseline of the cohort study. If there were women who in fact started using powders after the baseline, they would be incorrectly labelled as non-users. And, if there were indeed a risk associated with use of talc powders, the risk estimate would be diluted by the incorrect inclusion of users among non-users. Accordingly, the longer such subjects are followed, the more likely such misclassification is to occur.

The age at which information is collected is a relevant consideration. In most case-control studies, the mean age of the study subjects was between 50 and 60. In the NHS cohort study the mean age at baseline questionnaire was around 40 and in the WHI it was over 60. In each study, women were asked about their past history of powder usage. Clearly the WHI women had a further stretch of time to consider than the women of the NHS and even of the case-control studies.

A particular form of measurement error may well have occurred in the Gonzalez 2016 study and produced even more attenuation of RR estimates. Namely, in their brief questionnaire on talc exposure, the question was formulated to ask women about their use of powders in the 12 months preceding the interview. While exposure to talc over the past 12 months may be correlated with exposure over the entire etiologically relevant period, which might go back decades in the life of the woman, the correlation is probably weak, and this is another source of measurement error.

7.2.4 Short follow-up periods for disease ascertainment

This is a potential source of bias that would affect cohort studies.

In a cohort study, if the period of follow-up after baseline is relatively short; and if the latency period between exposure and cancer is long, the excess risk may not be detectable because cases that would occur after long latency have not had time to occur. If this did occur, it would lead to an artificially low RR estimate.

This could have been an issue in the initial publication from the NHS, the Gertig 2000 paper. As of the Gates 2008 and Gates 2010 analyses of the NHS, the follow-up period was probably long enough and this bias should have abated. For the WHI study it was likely an issue in the Houghton 2014 paper, and it would remain so until there is much longer follow-up. It would also be an issue in the Gonzalez 2016 paper from the Sister Study, which had only 6 years of follow-up after exposure was ascertained.

7.2.5 Diagnostic error

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

The diagnosis of cancer is never error-free. And details of histology and staging are even more error-prone. Further, there are trends in diagnostic criteria and methods over time, as well as in the terminology and classifications used. So what we observe in these various studies of ovarian cancer represents imperfect estimates of true biologic/pathologic status. The impact of such “errors” is mainly the same as exposure measurement error, namely it would tend to artificially reduce RR estimates. Since most case-control studies start from hospital-based cancer diagnoses as the point of entry, they usually have reasonably valid diagnostic information.

In general, cohort studies tend to be more vulnerable to this source of error and bias, because disease diagnosis information is often obtained from sub-optimal sources, such as the information provided by the study subject or her family, or information obtained from death certificates. In the three cohort studies included in the meta-analysis, there were high quality verifications of diagnostic information that had been provided by the women or their families. But such verification may not be as reliable as information coming straight from hospital pathology or oncology services. I expect that this was not a major issue here, but to the extent that it did operate, it too would have led to some additional attenuation of RR estimates, as I explained above.

7.2.6 Initiation of powdering as a result of ovarian cancer

This is a potential source of bias that would affect case-control studies.

It has been speculated that women with early symptoms of ovarian cancer might take up the use of powders to help with relief of their symptoms. If so they might report that they used powders before their cancer was diagnosed and this could artificially inflate the RRs. While the women are usually questioned about the period before their cancer was diagnosed, there could be some “telescoping” so that women who start dusting after diagnosis respond in the affirmative to the questionnaire.

In the same vein, it has been speculated that treatment for ovarian cancer might produce side effects that could be relieved by powdering. And again, it might be posited that women ignore the instruction to refer the exposure question to the time before the onset of the cancer.

If the early symptoms of ovarian cancer provoke some women to start dusting the perineum to relieve some of the discomfort, or if the treatment provokes women to start dusting, this would lead to an artefactual excess RR.

I have not found any empirical evidence to support this hypothesis.

In the few datasets I have seen which describe the age distribution of initiation of powdering, there were very few patients who started in the year or two before diagnosis of the cancer. I am inclined to believe that it is virtually a non-issue, and that if it operated at all, it would only have operated on a handful of the thousands of women who were part of the various case-control studies.

7.2.7 Confounding

This is a potential source of bias that would affect both case-control and cohort studies.

If women who use powders are also more likely to be exposed to other risk factors for ovarian cancer, then it might distort the relationship between powdering and OC. The direction and the degree of distortion (bias) that would be induced depends on two components, a) the true association between the confounder and ovarian cancer, and b) the association between the confounder and dusting behaviour. Thus, depending on the direction of these two component associations, the confounding can result in artificially decreased or increased RRs. Typically, the degree of confounding is much lower than the strength of the association between the confounder and ovarian cancer. In order for a confounder to induce an artificial RR of 1.25 for dusting, it would have to have an RR much greater than 1.25 with ovarian cancer and a fairly strong correlation with dusting behaviour. Given that the main studies have controlled for the main risk factors, I consider it unlikely that this operates. Table 1 shows the covariates that were controlled for in each study, and while there is some variability between studies in the list of covariates, the main known potential confounders (age, BMI or weight, parity) have been controlled for in almost all studies. It should be noted that while smoking is a well-established risk factor for many types of cancer, it is not a risk factor for ovarian cancer; thus, there is no need to control for smoking status in studies of ovarian cancer.

A thorough and reliable investigation of potential confounders was conducted by Cramer (2016); in the large database of New England-based studies, they explored the potential confounding effect of a host of personal characteristics including demographic, reproductive, hormonal, comorbidities, activities, and exposures. None of the covariates that they explored had any meaningful confounding effect on the association between talc and ovarian cancer.

7.2.8 Publication bias

This is a potential source of bias that would affect case-control and cohort studies.

This refers to the tendency for some evidence never to “see the light of day”. Namely, when results are “negative” or “null”, it may be that investigators never bother to submit them for publication, or alternatively, that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small. In the talc-ovarian cancer literature this would have been more likely in the pre-2000 era when there was much less scientific interest in the hypothesis linking talc to ovarian cancer. As a sensitivity analysis, I conducted a meta-analysis on the subset of studies in Table 2 that had at least 20 exposed cases. That is, I eliminated the studies from that stratum of the universe of studies that were most susceptible to publication bias. The resulting meta-RR was almost identical to those shown in Table 4. Because this has been a somewhat controversial topic in epidemiologic circles over the past 20 years, I doubt if there were large important studies with null findings on talc-ovarian cancer that went unpublished.

In their meta-analyses, Berge 2018 and Pennikilampi 2018 both showed funnel plots of the results. These are meant to detect so-called publication bias. Both of those analyses concluded that there was no publication bias.

In summary, I consider that the observed association between talc and ovarian cancer is not an artefact due to publication bias.

7.2.9 Summary comments regarding biases and errors

While the results of epidemiologic studies strongly supports the hypothesis of an association between perineal use of powders and risk of ovarian cancer, we must be wary of potential sources of error and bias that can distort an association before concluding that this association is causal. I have therefore gone through the plausible sources and types of error and bias that could potentially explain the positive association seen across the relevant studies to ascertain how likely it is that each such type was actually operative and, if so, what the nature of the impact may have been. These evaluations are based on my professional opinion as an epidemiologist having conducted, reviewed, and evaluated many hundreds if not thousands of epidemiologic studies.

Of the various types of error listed, some could artificially inflate the RR estimates and some could artificially decrease the RR estimates. Some are likely to have occurred and some are unlikely to have occurred. The one that certainly occurred and that has a non-trivial attenuating effect on RRs is random exposure misclassification (section 7.2.3). As explained above, if there is a true association, then the true RR is almost certainly greater than the estimates seen in these studies and in the resulting meta-analyses. Other types of error and bias that are highly likely to have occurred are the two that are specific to cohort studies. Namely, the Nurses' Health Study papers (Gates 2008 and Gates 2010) almost certainly suffered from an attenuated RR estimate because of the compromised reference category of "unexposed" while the Women's Health Initiative paper (Houghton 2014) and the Sister Study paper (Gonzalez 2016) almost certainly suffered from a too short follow-up period (section 7.2.4). In my opinion, the occurrence and the possible impact of other listed types of bias and error are more speculative, and less likely.

Consequently, in my opinion, the observed association between talcum powder products and ovarian cancer is unlikely to be explained by any methodological problems with the studies.

8. Bradford Hill guidelines applied to talc and ovarian cancer

The Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) states: "There is no formula or algorithm that can be used to assess whether a causal inference is

appropriate based on these guidelines.” These guidelines are simply aspects that might be considered in assessing causality. I will give my assessment of how the evidence regarding talcum powder products and ovarian cancer fit into those aspects. I will use the version listed in the Reference Manual on Scientific Evidence. While there is no objective basis or scientific precedent or “scientific jurisprudence” for quantification or weighting of the various “aspects”, to help the reader to understand the relevance that I attached to each “aspect” in my evaluation, I will provide an informal ranking of the importance that I attach to each aspect, in the specific context of the assessment of causality of evidence regarding talcum powder products and ovarian cancer. I will list the aspects in descending order of importance that I attach to them.

My opinions are briefly summarized in **Table 12**.

Highly important aspects in my weighting

There is a set of B-H aspects that are utterly inter-related and cannot be disassociated one from the other. In combination, they represent the most important aspect to consider in evaluation of causality of talcum powder for ovarian cancer. These include strength of association, dose-response, consideration of biases, and consistency of findings.

Strength of the association. This can embody both the magnitude of the RR and its statistical significance. The meta-RR estimate is 1.28. That means that the best estimate from the epidemiologic literature is that women who regularly used talcum powder products in the genital area had 28% higher risk of ovarian cancer than women who did not use such powders. As I illustrate in Table 11 with a few examples, this RR is in line with many well-recognized risk factors for cancer and other diseases. For example, it is well accepted now that people living in an urban neighborhood in which the air is highly polluted with particulate matter have between 5% and 10% excess risk of lung cancer compared with people living in a less polluted urban neighborhood. Also, it is well accepted now that workers exposed to a solvent called trichloroethylene have about a 40% higher risk of kidney cancer compared with workers not exposed to trichloroethylene. Thus, the 28% increase of ovarian cancer for women who used talcum powders is in line with many recognized risk factors. This increased risk as manifested by the meta-RR is highly

statistically significant. (Note that the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts.) Such a high and significant meta-RR could not have occurred by chance. This is a very important factor in how I view the evidence of causality, and it supports causality.

Dose-response relationship. If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency). The most sensitive of these metrics is the cumulative amount. I evaluated the published studies reported on risks according to the different metrics. By far, the most important set of results on dose-response is that from the Terry 2013 pooled analysis of 10 studies using the cumulative exposure metric. And, the next most important from a statistical weight point of view is that from Schildkraut 2016. In both of those studies, there is a clear indication of increasing risk with increasing cumulative exposure. Since the statistical power to detect a trend is less than the power to detect an overall risk, it is not surprising that the p-value for trend does not attain the conventional 0.05 level, but it remains true that these studies support a dose-response. This is an important consideration in my assessment of causality, and the evidence on dose-response that our IARC committee had available in 2006 was much less persuasive than the evidence available now.

Consideration of alternative explanations - absence of bias. There are many potential sources of bias in observational research, including in epidemiology. It is important to consider the presence of bias in each study performed or reviewed in an evaluation of causality. The possibility of bias is so multifaceted that it is impossible to reliably assign an explicit score to the likelihood of bias in a study or in a body of studies. It is also important to understand that identifying a potential source of bias is not tantamount to identifying the presence of bias. In section 7.2, I have reviewed the potential role of several types of biases and errors

that can bedevil such research. I concluded there that none of those factors would cause the apparent associations.

Consistency of findings between studies (or replication of findings). Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship. In my review of the published epidemiological studies and meta-analysis, I am impressed by the consistently elevated risk across studies. Almost all of the 30 or so studies have produced an RR greater than the null (neutral) value of 1.0. If there really were no association between talcum powder use and ovarian cancer, we would expect to see as many RRs lower than 1.0 as higher than 1.0. The pattern we see is like flipping a coin 30 times and getting a heads 28 or 29 times. The individual study RRs are not all necessarily statistically significant, but that is irrelevant because most individual studies did not have sufficient statistical power to detect RR in the range of 1.2-1.4. It is the statistical significance of the meta-RR, representing the combined evidence that has the requisite power, and that excess RR is highly statistically significant. I place great weight upon this evidence of causality and, here, believe it to be amongst the most important findings.

Moderately important aspects in my weighting

Temporal relationship. Exposure should be seen to have preceded disease. It is almost a logical truism. This is the only aspect that Bradford Hill considered to be necessary. In all of the studies I reviewed, the information elicited about talc exposure concerned the time period before cancer onset. Since it is so obviously important, the reader may wonder why I place lesser weight on this aspect. It is simply because the presence of this condition of temporality is so obvious in these studies.

Biological plausibility (coherence with existing knowledge). It is both conventional and natural to consider whether any putative association is biologically plausible. The notion of

biological plausibility is multi-faceted. In the case of talcum powder products and ovarian cancer, it can include such issues as: how such powders have been used, female anatomy and physiology, toxico-kinetics and toxicology of talc, in vitro and in vivo mechanisms of carcinogenesis, and others.

The first thing to note about this aspect that Bradford Hill listed is that it is called “biological plausibility”, not “biological proof”. That is, there was never any implication that a determination of causality should rest on a demonstrated proven biological mechanism. Hill was always reserved about this aspect, stating that it was not an essential prerequisite to establishing causality. As I have mentioned above, it has been common in the history of medicine and epidemiology for the elaboration of a validated biological mechanism to come much later than the discovery and demonstration of a causal association. Appendix C gives a handful of such examples but there are scores more.

Insofar as the issue of talcum powder products and ovarian cancer is concerned, there is evidence to support a few biologically plausible mechanisms. First of all, there are two possible routes that talcum powder products can take to reach the ovaries. There is published evidence that talcum powder products (and its constituents and contaminants) that are applied to the vaginal area can migrate from there to the fallopian tubes and ovaries (Venter 1979; Henderson 1986; Heller 1996) or to pelvic lymph nodes. (Cramer 2007) In addition, as has been hypothesized and partially demonstrated in the discussion of asbestos and ovarian cancer, such particles might reach the ovaries via inhalation and translocation. (Miserocchi 2008; IARC 2012) Once the particles reach the ovaries, carcinogenesis can be triggered by the inflammation engendered by the particles. (Ness 1999; Ness 2000) There is considerable evidence that inflammation is an important mechanism for carcinogenesis (Coussens and Werb 2002; Grivennikov 2010). Alternative plausible mechanisms of carcinogenicity include talc induced oxidative stress (Buz’Zard 2007; Saed 2017; Fletcher 2018), and genotoxicity (Shukla 2009).

The evidence that commercial cosmetic talcum powder products have been shown to contain asbestos, fibrous talc, and heavy metals (Blount 1991; Paoletti 1984; Longo et al 2017, Crowley report 2018) provides a reasonable basis for hypothesizing that these

chemicals may contribute to the carcinogenicity of the talcum powder products. Asbestos is a well-known carcinogen, as are chromium and nickel compounds. It is plausible that any of these, in contact with the ovaries, can be carcinogenic.

The fact that there are credible biologically plausible mechanisms by which talcum powder products can reach the upper genital tract causing an inflammatory response, along with the presence of asbestos fibres and other carcinogens is an important consideration in support of my opinion that the genital use of talcum powder products can cause ovarian cancer.

Aspects of lesser importance in my weighting

Cessation of exposure. It is rare that there is valid evidence available to assess the impact of cessation of exposure in an observational study. In the studies on talcum powder and ovarian cancer, there is no evidence one way or the other concerning the effect of cessation of exposure. This aspect is not applicable and I place almost no weight on it.

Specificity of the association. This aspect is premised on the notion that an agent-disease association is more likely to reflect a causal association if the agent is not also associated with other diseases. In the 1960's, this seemed like a reasonable argument. In light of evidence from the past 60 years, this argument is no longer made and this aspect has fallen out of usage with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

So, I do not place much stock in this aspect. However, if I did, I would have to say that genital exposure to talc is associated with ovarian cancer and no other morbidity, which supports the 'specificity' of the relationship."

Analogy

Hill argued that if the agent is similar to another agent that has been shown to be a cause of the disease, then the agent under investigation is more likely to be a cause. The fact that exposure to asbestos fibers can cause cancers in lung, larynx mesothelial tissue and ovaries (IARC 2012) can indicate that, by analogy, talc, which is similar in some respects, might be

able to induce carcinogenesis. Thus, there is an argument for an analogy between talc and asbestos. While this aspect supports causality in Hill's framework, I consider it much less important an aspect than the ones listed above.

Coherence with other types of knowledge: Coherence with other knowledge can encompass a multitude of possibilities. This aspect is both vague and very open-ended, with no real operational instruction on how to use it. Hill gave an example in his paper, but the example was only applicable to tobacco and lung cancer. This is an aspect that, if it can be demonstrated, can enhance the likelihood of causality, but its absence cannot detract from causality. I don't consider it to have much weight in this context.

9. Contrast with IARC Monograph and other reviews

The 2006 IARC Monograph meeting, which I chaired, found that a causal relationship was "possible" between perineal talc powder exposure and ovarian cancer. I concurred with that evaluation.

It is now my professional opinion, based on the totality of the evidence that, to a reasonable degree of scientific certainty, the causal relationship between perineal talc powder exposure and ovarian cancer is "probable. "

What has changed in the years since the IARC review?

The RR estimates in Table 2 are remarkably consistent in showing a highly statistically significant excess risk. The number of published study results and scientific literature addressing the epidemiology, toxicology, molecular biology, and mechanistic studies has increased since 2006, and the evidence of excess risk has been consistently demonstrated across the past three decades.

The various possible biases that are on the table remain substantially similar to the ones that were considered by the IARC panel. At the time, we were not convinced that the apparent excess risk could be explained by those potential biases or confounding. As stated above, my review of the relevant studies and potential biases has led me to conclude that bias does not explain the consistent increased risks seen across the credible studies.

There is important new information with regard to the issue of dose-response. Contrary to the impression that the IARC panel had of a total absence of dose-response, and even a possible trend in the opposite direction, the results of three recent publications, Terry 2013 and Schildkraut 2016, using cumulative exposure metrics, and Wu 2015 using duration of exposure, all demonstrate a clear compatibility with a dose-response relationship. The recent meta-analysis of Berge 2018 supports the presence of dose-response in both duration and frequency of use. The most convincing of these is the Terry 2013 pooled analysis, which assembled a larger dataset than all other attempts to assess dose-response combined. Clearly, earlier reviews could not have integrated the results from these recent studies.

It is my opinion, based upon the above the data, there is evidence of a dose-response relationship. Penninkilampi 2018 has recently expressed a similar opinion.

10. Conclusion

The totality of evidence demonstrates that perineal or genital use of talcum powder products is associated with ovarian cancer. Based on contemporary data, my estimated RR between ever perineal use of talc powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). The body of epidemiologic evidence is remarkably consistent in demonstrating an excess risk. The evidence summarized in Table 6 is compatible with the presence of a dose-response relationship between cumulative exposure to talcum powder products and ovarian cancer. There are various potential sources of bias in these studies, some of which could have inflated the true RR estimate and some of which would have deflated the true RR estimate. Apart from random measurement error, which is inevitable in such studies and which tends to deflate the RR estimates, there is no certainty that the other potential biases were in fact operative and to what degree. It is my opinion, however, that neither bias nor confounding explains the consistent positive association seen across studies. Additionally, there are biologically plausible mechanisms by which talcum powder products can cause ovarian cancer.

Based on the totality of the evidence, it is my opinion, to a reasonable degree of scientific certainty, that the perineal use of talcum powder products can cause ovarian cancer. Given the seriousness of ovarian cancer and its associated morbidity, this causal risk represents an important public health issue.

11. Tables

Table 1. Steps in my evaluation of general causation between talcum powder product use and ovarian cancer

1. Identify all epidemiology study papers that present results on talc and Ovarian Cancer.
2. Extract all RR results from every paper into a database.
3. Determine which of the papers and results present truly independent relevant results.
4. Extract from each study the RR for Ever/Never use of talc in the genital area in relation to OC risk.
5. Conduct a Meta-analysis.
6. Examine the evidence about a possible dose-response relationship.
7. Consider issues of bias, confounding and other sources of error in the various studies.
8. Consider relevant opinion pieces, review articles, and agency reports.
9. Consider opinions from experts regarding possible biological mechanisms.
10. Consider all relevant aspects of association to infer causation.
11. Write report.

Table 2. Relative risk estimates between ever regular use of talcum powders products¹ in the perineal area and ovarian cancer², from various studies used in the Main Meta-analysis or in one or more of seven sensitivity analyses

Author	Included in Main meta- analysis	Number exposed cases	All tumours	
			RR ³	95% CI ⁴
Booth 1989	?	141	1.29	0.92 1.80
Chen, 1992	?	7	3.9	0.91 10.6
Cook 1997	?	159	1.5	1.1 2.0
Cramer 1982	?	60	1.55	0.98 2.47
Cramer 2016		642	1.33	1.16 1.52
Gates 2008		57	1.24	0.83 1.83
Gates 2010	?	231 ⁵	1.06	0.89 1.28
Godard 1998	?	18	2.49	0.94 6.58
Gonzalez 2016	?	17	0.73	0.44 1.2
Harlow 1989	?	49	1.1	0.7 2.1
Harlow 1992	?	114	1.5	1.0 2.1
Hartge 1983	?	7	2.5	0.7 10.0

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Author	Included in Main meta- analysis	Number exposed cases	All tumours	
			RR ³	95% CI ⁴
Houghton 2014	?	181	1.12	0.92 1.36
Mills 2004	?	106	1.37	1.02 1.85
Ness 2000	?	161	1.5	1.1 2.0
Purdie 1995	?	467	1.27	1.04 1.54
Rosenblatt 1992	?	22	1.7	0.7 3.9
Schildkraut 2016 A ⁵	?	248	1.44	1.11 1.86
Schildkraut 2016 B ⁵		128	1.19	0.87 1.63
Shushan 1996		21	1.97	1.06 3.66
Terry 2013	?	2600	1.24	1.15 1.33
Terry-AUS 2013		705	1.13	0.92 1.38
Terry-DOV 2013		272	1.13	0.93 1.36
Terry-HAW 2013		74	0.99	0.70 1.41
Terry-HOP 2013		194	1.34	1.07 1.67
Terry-NCO 2013		195	1.37	1.05 1.80
Terry-NEC 2013		755	1.28	1.12 1.47
Terry-SON 2013		197	1.35	1.03 1.76

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Author	Included in Main meta-analysis	Number exposed cases	All tumours	
			RR ³	95% CI ⁴
Terry-USC 2013		208	1.36	1.06 1.74
Tzonou 1993	☐	6	1.05	0.28 3.98
Whittemore 1988	☐	67	1.36	0.91 2.04
Wong 1999	☐	157	1.0	0.8 1.3
Wu 2015	☐	701	1.46	1.27 1.69

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. In this table we report the result for all types of ovarian cancer combined. With the exception of the Harlow 1989 study that was restricted to borderline tumours, we have assumed that all studies included both borderline and invasive tumours, although this was not always clear in the publications.
3. RR or OR.
4. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
5. Estimated based on Table 1 of Gates 2010.
6. The Schildkraut 2016 case-control study presented two sets of results that both have some legitimacy for the present purpose. Schildkraut 2016A shows the results for all subjects who were interviewed in the study from 2010-2015. Schildkraut2016B shows the results for those subjects who were interviewed before 2014, and who, according to the authors, were not susceptible to having been tainted by publicity from a class action suit.

Table 3. Main meta-analysis and sensitivity analyses conducted on the association between ever regular use of talcum powder products in the perineal area and ovarian cancer (all types combined).

Studies in meta-analysis	N*	RR-estimate			Heterogeneity	
		Meta-RR	95% CI	p-value	I ²	p-value
<i>Main Meta-Analysis - list in Figure 1 Forest plot</i>	21	1.28	1.19 1.38	0.00	32.9	0.07
<i>Sensitivity analyses</i>						
Substitute Gates 2008 for Gates 2010	21	1.30	1.21 1.40	0.00	22.9	0.16
Substitute Schildkraut B for Schildkraut A	21	1.27	1.17 1.37	0.00	30.8	0.08
Add Shushan	22	1.29	1.19 1.39	0.00	33.8	0.06
Substitute List A** for Terry	27	1.27	1.19 1.35	0.00	26.2	0.10
Substitute List A for Terry and Gates 2008 for Gates 2010	27	1.29	1.21 1.37	0.00	16.6	0.22
Substitute List A for Terry and Schildkraut B for Schildkraut A	27	1.26	1.18 1.34	0.00	24.5	0.12
Substitute List A for Terry and add Shushan	28	1.28	1.20 1.36	0.00	27.4	0.09

*N: Number of RRs that went into the meta-analysis. This is not synonymous with the number of studies because some RRs (e.g. Terry 2013, Cramer 2016) embody multiple studies.

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**List A studies: Cramer 2016; Wu 2015; Terry-Aus 2013; Terry-DOV 2013; Terry-Haw 2013; Terry-HOP 2013; Terry-NCO
2013; Terry SON 2013

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Table 4. Comparison of results of three contemporaneous and independent meta-analyses of the association between ever regular use of talcum powder products in the perineal area and ovarian cancer.

Meta-analysis author	N*	Meta-RR	95% CI	Heterogeneity p-value
Siemiatycki 2018	21	1.28	1.19-1.38	0.07
Berge 2018	27	1.22	1.13-1.30	0.02
Penninkilompi 2018	26	1.35	1.24-1.39	0.31

* Number of published RR estimates that went into the meta-analysis. This does not necessarily correspond to the number of studies, since, for example, the Terry 2013 pooled estimate used in the Siemiatycki meta-analysis embodied 10 studies.

Table 5. Relative risk estimates between ever regular use of talcum powder products on sanitary napkins and ovarian cancer, and results of meta-analysis.

Author	Number exposed cases	RR ¹	95% CI ²
Chang 1997	51	1.26	0.81 1.96
Cook 1997	38	0.9	0.5 1.5
Cramer 1999	20	1.45	0.68 3.09
Gertig 2000	32	0.89	0.61 1.28
Harlow 1989	8	2.6	0.9 22.4 ²
Harlow 1992	9	1.1	0.4 2.8
Houghton 2014	93	0.95	0.76 1.20
Ness 2000	77	1.6	1.1 2.3
Rosenblatt 1992	21	4.8	1.3 17.8
Rosenblatt 2011	55	0.82	0.58 1.16
Whittemore 1988	5	0.62	0.21 1.80
Wong 1999	13	0.9	0.4 2.0
Meta-analysis		1.08	0.89 1.31
p-value for heterogeneity = 0.09			

1. RR or OR.
2. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.

Table 6. Relative risk estimates between subgroups defined by cumulative exposure measures¹ and ovarian cancer², from various studies.

Author	Cumulative applications ³	Number exposed cases	RR ⁴	95% C.I.	
Cook 1997 ⁴	< 2000	20	1.8	0.9	3.5
	2001-5000	24	1.6	0.9	2.9
	5001-10000	21	1.2	0.6	2.4
	>10000	28	1.8	0.9	3.4
Harlow 1992	<1000	18	1.3	0.7	2.7
	1000-10000	54	1.5	0.9	2.4
	>10000	42	1.8	1.0	3.0
Mills 2004	Quartile 1	18	1.0	0.6	1.8
	Quartile 2	28	1.8	1.1	3.0
	Quartile 3	34	1.7	1.1	2.7
	Quartile 4	20	1.1	0.6	1.8
	10000+	18	0.87	0.48	1.57
Schildkraut 2016	≤3600	92	1.16	0.83	1.63
	>3600	152	1.67	1.23	2.26
Terry 2013 ⁵	Quartile 1	534	1.14	1.00	1.31
	Quartile 2	541	1.23	1.08	1.41
	Quartile 3	542	1.22	1.07	1.40
	Quartile 4	586	1.32	1.16	1.52

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a cumulative measure. All of these were case control studies.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. For the Cook study the metric was the number of days on which the woman had ever applied the powder. For the other studies the metric is based on an estimate of the total number of applications.

4. RR or OR.
5. This study was based on a pooling of studies from 8 teams. Two of the teams (Cramer 2016 and Rosenblatt 2011) published separate analyses of risk by cumulative number of applications. But these are not shown here because they are rendered redundant by the Terry 2013 pooled results.

Table 7. Relative risk estimates between subgroups defined by duration of use¹ and ovarian cancer², from various studies.

Author	Duration of use	Number exposed cases	RR ⁴	95% C.I.	
Chang 1997	<30	60	1.7	1.1	2.6
	30-40	71	1.4	1.0	2.2
	>40	41	0.9	0.5	1.4
Cramer 1999	<20 years	55	1.9	1.2	3.0
	20-30 years	32	1.3	0.8	2.3
	>30 years	59	1.4	0.9	2.3
Cramer 2016	< 8 years of use	133	1.31	1.03	1.68
	8-19 years of use	126	1.31	1.02	1.68
	20-35 years of use	147	1.35	1.07	1.70
	>35 years of use	129	1.33	1.03	1.71
Harlow 1992	<10 years	14	1.2	0.5	2.6
	10-29 years	49	1.6	1.0	2.7
	> 30 years	51	1.6	1.0	2.7
Houghton 2014	<9 years	135	1.09	0.88	1.36
	10+ years	97	1.02	0.80	1.30
Ness 2000	<1 year	17	2.0	1.0	4.0
	1-4 years	76	1.6	1.1	2.3
	5-9 years	40	1.1	0.8	1.9
	>10 years	233	1.2	1.0	1.5
Mills 2004	<3 years	18	1.0	0.6	1.8
	4-12 years	32	1.9	1.2	3.0
	13-30 years	29	1.5	0.9	2.3
	>30 years	21	1.2	0.7	2.1

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Author	Duration of use	Number exposed cases	RR ⁴	95% C.I.
Rosenblatt 2011	1-9 years	33	1.39	0.85 2.28
	10-19 years	29	1.46	0.87 2.45
	20-34 years	30	1.28	0.78 2.10
	35+ years	19	0.91	0.51 1.62
Schildkraut 2016	≤20 years	101	1.33	0.95 1.86
	>20 years	144	1.52	1.11 2.07
Whittemore 1988	1-9 years	34	1.6	1.0 2.6
	10+	50	1.1	0.7 1.7
Wong 1999	1-9 years	39	0.9	0.6 1.5
	10-19 years	49	1.4	0.9 2.2
	>20 years	101	0.9	0.6 1.2
Wu 2015	Per 5 years of exposure	1273	1.14	1.09 1.20

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of duration.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR.

Table 8. Relative risk estimates between subgroups defined by measures of frequency of use¹ and ovarian cancer², from various studies.

Author	Frequency of use	Number exposed cases	RR ⁴	95% C.I.	
Booth 1989	Rarely	6	0.9	0.3	2.4
	Monthly	7	0.7	0.3	1.8
	Weekly	57	2.0	1.3	3.4
	Daily	71	1.3	0.8	1.9
Chang 1997	<10 per month	76	1.8	1.2	2.7
	10-25 per month	54	1.1	0.7	1.7
	Per 10 applications per month		0.9	0.7	1.1
Cramer 1999	<30 per month	64	2.2	1.4	3.6
	30-39 per month	59	1.7	0.8	1.8
	≥40 per month	23	1.7	0.8	3.1
Cramer 2016	1-7 days per month	220	1.17	0.96	1.44
	8-29 days per month	110	1.37	1.05	1.78
	>30 days per month	205	1.46	1.20	1.78
Gates 2008	<1 per week	18	0.98	0.54	1.79
	1-6 per week	22	1.01	0.57	1.79
	Daily	35	1.44	0.88	2.37
Harlow 1992	<5 per month	32	1.5	0.8	2.7
	5-29 per month	24	1.2	0.6	2.2
	≥30 per month	58	1.8	1.1	3.0

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Author	Frequency of use	Number exposed cases	RR ⁴	95% C.I.
Mills 2004	<1 per week	34	1.3	0.9 2.1
	1-3 per week	31	1.6	0.7 1.8
	4-7 per week	41	1.7	1.1 2.6
Schildkraut 2016	<Daily	88	1.12	0.80 1.58
	Daily	158	1.71	1.26 2.33
Whittemore 1988	1-20 per month	41	1.3	0.8 2.0
	>20 per month	44	1.5	0.9 2.2

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of frequency of use.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR

Table 9. Relative risk estimates between ever regular use of talcum powder products¹ in the perineal area and invasive serous ovarian cancer, from various studies.

Author	Number exposed cases	RR ²	95% CI ³
Cook 1997	71	1.7	1.1 2.5
Gates 2010	131 ⁴	1.06	0.84 1.35
Harlow 1992	60	1.4	0.9 2.2
Houghton 2014	105	1.13	0.84 1.51
Mills 2004	42	1.77	1.12 2.81
Schildkraut 2016	165	1.38	1.03 1.85
Terry 2013	1197	1.24	1.13 1.35
Wong 1999	136	1.2	0.7 2.1
Meta-analysis		1.25	1.15 1.36

p-value for heterogeneity 0.06

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. RR or OR.
3. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
4. Estimated based on Table 1 of Gates 2010.

Table 10. Some major misconceptions in reviewing evidence on talc and ovarian cancer

1. Cohort studies are more valid and informative than case-control studies.
2. Hospital-based case-control studies are more valid and informative than the population-based case-control studies.
3. Counting the number of “statistically significant” results is a valid way of assessing the consistency of results among multiple studies.
4. If a product has been used for a long time, it must be safe
5. You cannot prove causality with an RR less than 2.0.
6. Government agencies provide a reliable up-to-date source of scientific information.
7. A biological mechanism must be proven before we can establish causality
8. Bradford-Hill “aspects” represent a recipe list of necessary ingredients.

Table 11. Selected examples of some of the recognized causal associations that have RR less than 2.0

Agent	Disease	Approximate RR
Urban air pollution	Lung cancer	1.09 ¹
Trichloroethylene	Kidney cancer	1.32 ²
Diesel engine emissions	Lung cancer	1.42 ³
Benzene	Leukemia	1.72 ⁴
Domestic radon gas	Lung cancer	1.29 ⁵
Second hand cigarette smoke	Lung cancer	1.64
Intermittent intense sun exposure	Melanoma of the skin	1.61 ⁶
Estrogen-progestin menopausal therapy	Breast cancer	1.59 ⁷

¹ Hamra GB, Guha N, Cohen A, et al (2014). Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis, *Environ Health Perspect* 122:906-911.

² Karami S, Lan Q, Rothman N, et al (2012). Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. *Occupational and Environmental Medicine* 69:858-867.

³ Mahjub H, Sadri G (2006). Meta-analysis of case-referent studies of specific environmental or occupational pollutants on lung cancer. *Indian Journal of Cancer* 43(4):169-173.

⁴ Khalade A, Jaakkola MS, Pukkala E, Jaakkola JJ (2010). Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environmental Health* 9(31):1-8.

⁵ Zhang Z-L, Sun J, Dong J-Y, et al (2012). Residential Radon and Lung Cancer Risk: An Updated Meta-analysis of Case-control Studies. *Asian Pac J Cancer Prev* 13:2459-2465.

⁶ Gandini S, Sera F, Cattaruzza MS, et al (2004). Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *European Journal of Cancer* 41:45-60.

⁷ Kim S, Ko Y, Lee HJ, Lim J (2018). Menopausal hormone therapy and the risk of breast cancer by histological type and race: a meta-analysis of randomized controlled trials and cohort studies. *Breast Cancer Research and Treatment* 170(3):667-675.

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Cigarette smoking	Cardiovascular disease	1.6 ⁸
Physically inactive (compared with physically active) ⁹	Hypertension	1.19
	Diabetes	1.12
Low fruit and vegetable diet	Cardiovascular disease	1.09 ¹⁰

⁸ Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on British male doctors, *British Medical Journal*, 328(7455):1519.

⁹ Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs, Jr DR, Liu K (2003). Cardiorespiratory Fitness in Young Adulthood and the Development of Cardiovascular Disease Risk Factors. *JAMA*, 290(23):3092-3100

¹⁰ Aune D, Giovannucci E, Boffetta P, Fadnes L, Keum N, Norat T, Greenwood D, Riboli E, Vatten L, Tonstad S (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality - a systematic review and dose-response meta-analysis of prospective studies, *International Journal of Epidemiology* 43(3):1029-1056. (This RR estimate is computed from the reciprocal of the High fruit and vegetable variable that was reported by the authors. That is, 1/0.92).

Table 12. Bradford Hill aspects in relation to perineal talc exposure and ovarian cancer

Aspect	Brief comment	Weight in evaluating causality
Strength of the association	There are stronger associations and there are weaker associations	High
Dose response relationship	Reasonably clear increase in risk with increasing exposure	High
Consideration of alternative explanations – absence of bias	Yes considered, and none is compelling	High
Replication of the findings	Very strong, almost all studies support association	High
Temporal relationship	Exposure preceded disease in all studies	Moderate
Biological plausibility	There are plausible mechanisms	Moderate
Cessation of exposure	Not applicable.	Less
Specificity of the association	Yes, talc is not associated with a multitude of diseases	Less
Coherence with other knowledge	Could be similar to asbestos carcinogenicity	Less
Analogy		Less

12. Figures

Figure 1. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talc powder in the perineal area, based on all informative studies, studies ordered by magnitude of RR.

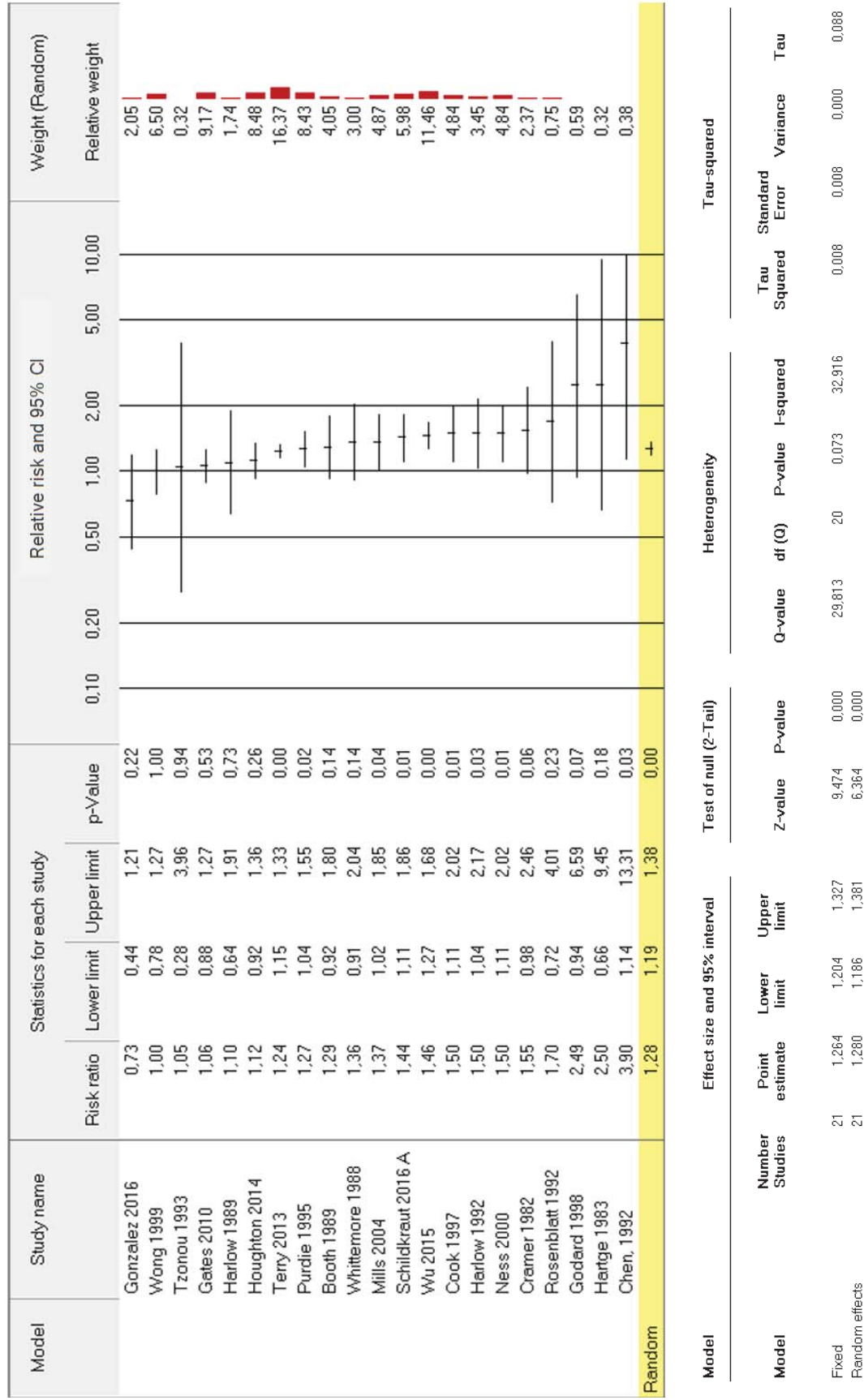


Figure 2. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talcum powder products on sanitary napkins, based on all informative studies.

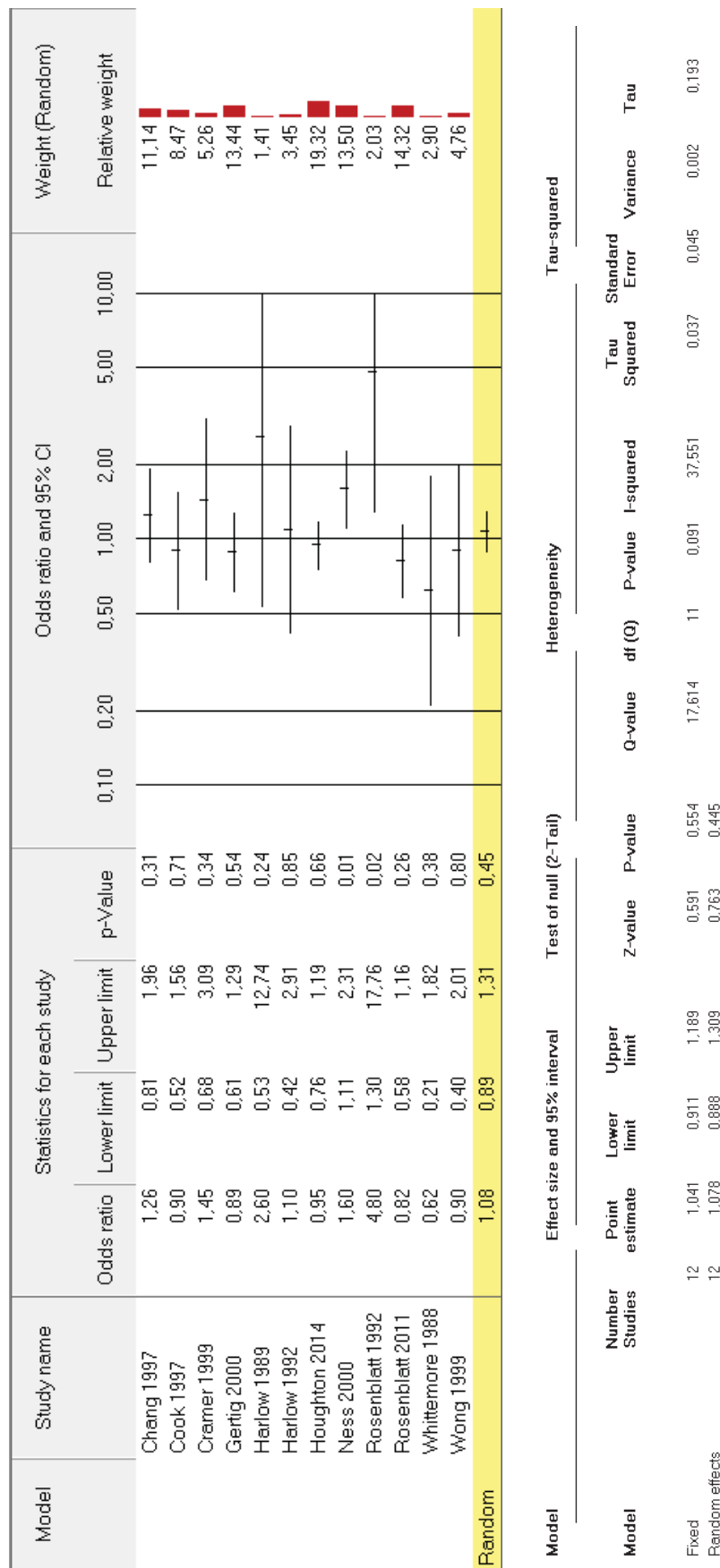
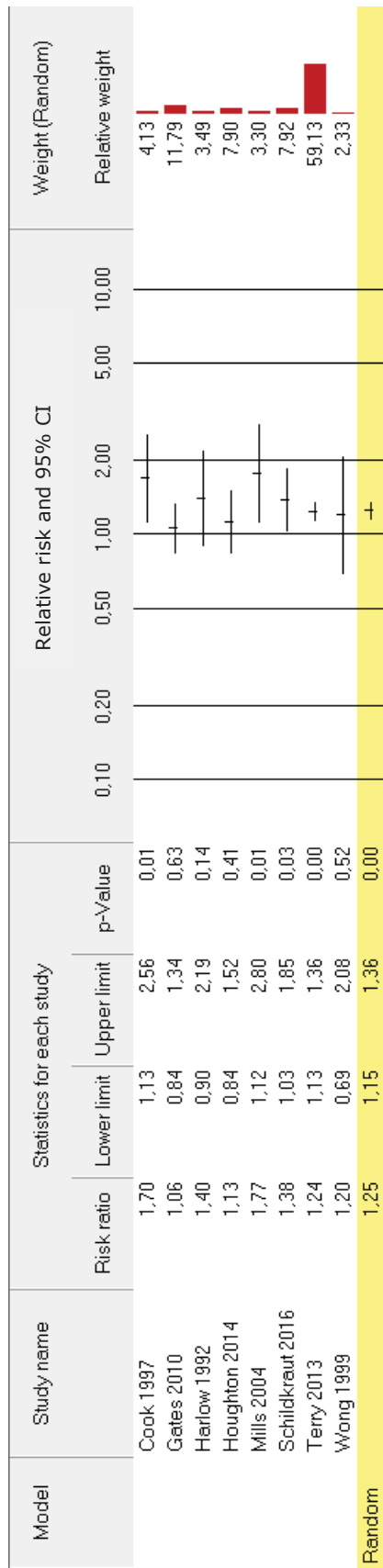


Figure 3. Meta-analysis of relative risk of invasive serous ovarian cancer among women who regularly used talcum powder products in the perineal area, based on all informative studies



Model	Effect size and 95% interval			Test of null (2-Tail)			Heterogeneity			Tau-squared		
	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error
Fixed	8	1.250	1.161	1.345	5.963	0.000	7.401	7	0.388	5.422	0.001	0.011
Random effects	8	1.254	1.152	1.364	5.249	0.000					0.000	0.033

13. Appendix A

Appendix Table A1. Papers that contain some results on the association between exposure to perineal talc and ovarian cancer, and whether the paper was included in my meta-analyses of the binary Ever/Never exposed variable

Author	Included/excluded	Reasons for exclusion
Booth 1989	Core Inclusion	
Chang 1997	Core Inclusion	
Chen 1992	Core Inclusion	
Cook 1997	Core Inclusion	
Cramer 1982	Core Inclusion	
Cramer 1995	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 1999	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2005	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2016	Excluded when Terry 2013 is included	Considerable overlap between this and the Terry 2013 NEC component
Eltabbakh 1998	Excluded	Cases were peritoneal cancer and controls were ovarian cancer
Gates 2008 ²	Included in one sensitivity analysis	Overlap with Gates 2010

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Author	Included/excluded	Reasons for exclusion
Gates 2010 ²	Included in all analyses except one sensitivity analysis	This may be a more complete analysis than Gates 2008, but the degree of overlap is unclear.
Gertig 2000	Excluded	Subsumed in Gates 2008 and Gates 2010
Godard 1998	Core inclusion	
Gonzalez 2016	Core inclusion	
Green 1997	Excluded	This appears to be an analysis of a subset of the subjects in Purdie 1995
Hankinson 1993	Excluded	Numerical results were not presented.
Harlow 1989	Core inclusion	
Harlow 1992	Core inclusion	
Hartge 1983	Core inclusion	
Houghton 2014	Core inclusion	
Jordan 2007	Excluded	Benign tumours only
Kurta 2012	Excluded	Included in Terry 2013
Langseth 2004	Excluded	Not based on perineal application of cosmetic powder.
Lo-Ciganic 2012	Excluded	Same study as Kurta 2012 and included in Terry 2013.
Merrit 2008	Excluded	Included in Terry 2013

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Author	Included/excluded	Reasons for exclusion
Mills 2004	Core inclusion	
Moorman 2009	Excluded	Included in Terry 2013
Pike 2004	Excluded	Included in Terry 2013
Purdie 1995	Core inclusion	
Ness 2000	Core inclusion	
Rosenblatt 1992	Core inclusion	
Rosenblatt 2011	Core inclusion	
Schildkraut 2016	Core inclusion	
Shushan 1996	Included in sensitivity analysis	Unclear on how they obtained data on talc exposure or what the route of exposure was
Terry 2013	Included in Main analysis, but replaced by component studies in sensitivity analyses	
Tzonou 1983	Core inclusion	
Whittemore 1988	Core inclusion	
Wong 1999	Core inclusion	
Wu 2015	Core inclusion	

Appendix Table A2. Some administrative and contextual information on the studies used in the following tables

Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Booth 1989	London, Oxford UK	1978-1983	Case-control; Hospital controls
Chen 1992	Beijing Cancer Registry	1984-1986	Case-control; Population controls
Cook 1997	Washington State	1986-1988	Case-control; Population controls
Cramer 1982	Boston	1978-1981	Case-control; Population controls
Cramer 2016	New England	1992-2008	Case-control; Population controls
Gates 2008 ²	USA – NHS study	1976-2004	Case-control nested in Cohort (US nurses)
Gates 2010 ²	USA – pooled 2 cohorts of nurses NHS and NHSII	1976-2004 1989-2005	Cohort (US Nurses)
Godard 1998	Montreal, Canada	1995-1996	Case-control; Population controls
Gonzalez 2016	Puerto Rico and 11 States USA	2003-2014	Cohort
Harlow 1989	Washington State	1980-1985	Case-control; Population controls
Harlow 1992	Boston	1984-1987	Case-control; Population controls

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Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Hartge 1983	Washington, DC	1974-77	Case-control; Population controls
Houghton 2014	USA	1993-2012	Cohort (WHI)
Mills 2004	California	2000-2001	Case-control; Population controls
Ness 2000	Pennsylvania, New Jersey, Delaware	1994-1998	Case-control; Population controls
Purdie 1995	Australia	1990-1993	Case-control; Population controls
Rosenblatt 1992	Baltimore	1981-1985	Case-control; Hospital controls
Schildkraut 2016	USA	2010-2015	Case-control; Population controls
Shushan 1996	Israel	1990-1993	Case-control Population controls
Terry 2013	Pooled 8 studies: USA & Australia	1984-2008	Case-control; Population controls
Terry-AUS 2013	Australia	2002-2006	Case-control Population controls
Terry – DOV ³ 2013	Washington State	2002-2009	Case-control Population controls
Terry – HAW 2013	Hawaii	1993-2008	Case-control Population controls

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Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Terry – HOP 2013	Pennsylvania, Ohio, Western NY State	2003-2008	Case-control Population controls
Terry – NCO 2013	North Carolina	1999-2008	Case-control Population controls
Terry – NEC 2013	Massachusetts, New Hampshire	1992-2006	Case-control Population controls
Terry – SON 2013	Southern Ontario	1989-1992	Case-control Population controls
Terry – USC 2013	Los Angeles County	1992-1998	Case-control Population controls
Tzonou 1983	Athens	1989-1991	Case-control; Controls – hospital visitors
Whittemore 1988	San Francisco	1983-1985	Case-control; Hospital & population controls
Wong 1999	Buffalo	1982-1992	Case-control; Hospital controls
Wu 2015	Los Angeles County	1992-2008	Case-control; Population controls

1.	Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
2.	The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.
3.	Terry – DOV 2013: the information in Terry 2013 is updated information included in Rosenblatt 2011.

Appendix Table A3. Covariates used in the analyses and exposure variables in the studies used in the following tables.

Author	Exposure variable selected	Covariates used in analysis
Booth 1989	At least monthly use	Since the authors did not present results for “ever” exposed, I calculated the OR from crude numbers in their tables. Therefore the OR presented is a crude one. However, results presented in Table 7 adjusted for age and social class
Chen 1992	Dusting perineum or lower abdomen > 3 months	Education
Cook 1997	Lifetime perineal application	Age
Cramer 1982	Any use as dusting powder and/or on sanitary napkins	Parity; menopausal status
Cramer 2016	Any talc use	Age; study center (MA, NH); BMI; primary relative with breast or ovarian cancer; parity; OC use; tubal ligation
Gates 2008 ¹	Regular genital talc use (1 per week or more)	Age; OC ² use; parity; BMI; post-menopausal hormone use
Gates 2010 ¹	Regular genital talc use (1 per week or more)	Age; BMI; physical activity; smoking; family history of breast or ovarian ca; OC use; tubal ligation; hysterectomy; age menopause; estrogen use
Godard 1998	Ever use of talc on perineum	Age; reproductive factors; OC use; tubal ligation; alcohol use; breast and abdominal surgery
Gonzalez 2016	Talc use in the past 12 months	Race; body mass index; parity; duration of oral contraceptive use; baseline menopause status; and patency

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Author	Exposure variable selected	Covariates used in analysis
Harlow 1989	Any genital talc use	Age; county; parity; OC use
Harlow 1992	Any genital talc use	Age; county; parity; marital status; education; religion; weight; use of sanitary napkins; douching
Hartge 1983	Any genital talc use	Race; age; gravidity
Houghton 2014	Combined use: longest duration of use among the applications to genitals, sanitary napkins and diaphragms	Age; race; OC use; HRT ³ use; family history of ovarian ca; age at last birth; BMI; smoking; tubal ligation; parity
Mills 2004	Ever use of talcum powder in genital area	Age; race/ethnicity; OC use; breast-feeding
Ness 2000	Genital rectal talc use	Age; parity; family history of ovarian ca;
Purdie 1995	Ever used talc in perineal region	Age; parity; duration of OC use; education; BMI; smoking; family history of ovarian ca
Rosenblatt 1992	Ever use of bath talc	Number of live births
Schildkraut 2016	Regular use of talc, cornstarch, baby or deodorising powder – at least once a month for 6 months	Age at diagnosis/interview; study site; education; tubal ligation; parity; BMI duration of OC use first degree family history of breast or ovarian cancer; and interview year
Shushan 1996	Talc use – never, seldom, moderate, a lot	Crude OR

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Author	Exposure variable selected	Covariates used in analysis
Terry 2013 – all components of the pooled analysis	Genital powder use	Age; OC use; parity; BMI; tubal ligation; ethnicity; race; tubal ligation; hysterectomy; breastfeeding
Tzonou 1983	Ever use of talc in perineal region	Age; years of schooling; weight before onset of the disease; age at menarche; menopausal status and age at menopause; parity and age at first birth; tobacco smoking; coffee drinking; consumption of alcoholic beverages; hair dyeing; use of analgesics and tranquilizers/hypnotics
Whittemore 1988	Talcum powder used on any two of perineum, sanitary pads and diaphragm	Age; race; hospital; parity
Wong 1999	Ever use of talc on genital region or thighs	Age; income; education; geographic location; OC use; smoking; family history of ovarian ca; age at menarche; menopausal status; tubal ligation or hysterectomy
Wu 2015	Genital talc use >1 year	Age; race/ethnicity; interviewer; reproductive variables; sociodemographic variables; medical history; hormonal variables; BMI.

1. The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.
2. OC: oral contraceptive
3. HRT: hormone replacement therapy

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14. Appendix B

Comparison of studies used and results extracted from articles referenced in three different meta-analyses.*

Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
Booth 1989 1.30 (0.94-1.80)	<i>Booth 1989</i> <i>1.29 (0.92 - 1.80)</i>	<i>Booth 1989</i> <i>1.29 (0.92 - 1.80)</i>
Chang 1997 1.42 (1.08 – 1.86)	Chang 1997 1.35 (1.03 - 1.76)	
Chen, 1992 3.90 (1.43 – 10.60)	<i>Chen, 1992</i> <i>3.90 (0.91 - 10.60)</i>	<i>Chen, 1992</i> <i>3.90 (0.91 - 10.60)</i>
<i>Cook 1997</i> <i>1.50 (1.11 – 2.02)</i>	<i>Cook 1997</i> <i>1.50 (1.10 - 2.00)</i>	<i>Cook 1997</i> <i>1.50 (1.10 - 2.00)</i>
Cramer 1982 1.60 (1.21 – 2.12)	<i>Cramer 1982</i> <i>1.92 (1.27 - 2.89)</i>	<i>Cramer 1982</i> <i>1.92 (1.27 - 2.89)</i>
Cramer 2016 1.42 (1.03 – 1.95)	Cramer 2016 1.32 (1.14 - 1.50)	Cramer 2016 1.33 (1.16 – 1.52)
		Gates 2008 1.24 (0.83 - 1.83)
	<i>Gates 2010</i> <i>1.06 (0.89 - 1.28)</i>	<i>Gates 2010</i> <i>1.06 (0.89 - 1.28)</i>
Gertig 2000 1.09 (0.86 – 1.38)		

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Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
<i>Godard 1998</i> 2.49 (0.94 - 6.58)	<i>Godard 1998</i> 2.49 (0.94 - 6.58)	<i>Godard 1998</i> 2.49 (0.94 - 6.58)
<i>Gonzalez 2016</i> 0.73 (0.44 - 1.20)	<i>Gonzalez 2016</i> 0.73 (0.44 - 1.20)	<i>Gonzalez 2016</i> 0.73 (0.44 - 1.20)
Green 1997 1.30 (1.06 - 1.60)	Goodman 2008 0.99 (0.7 - 1.41)	
Harlow 1989 1.10 (0.58 - 2.10)	<i>Harlow 1989</i> 1.10 (0.70 - 2.10)	<i>Harlow 1989</i> 1.10 (0.70 - 2.10)
<i>Hartge 1983</i> 2.50 (0.66 - 9.45)	<i>Harlow 1992</i> 1.50 (1.00 - 2.10)	<i>Harlow 1992</i> 1.50 (1.00 - 2.10)
<i>Houghton 2014</i> 1.12 (0.92 - 1.36)	<i>Hartge 1983</i> 2.50 (0.70 - 10.00)	Hartge 1983 0.70 (0.40 - 1.10)
Kurta 2012 1.40 (1.16 - 1.69)	Houghton 2014 1.06 (0.87 - 1.28)	<i>Houghton 2014</i> 1.12 (0.92 - 1.36)
	Lo-Ciganic 2012 1.34 (1.07 - 1.66)	

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Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
Merritt 2008 1.17 (1.01 - 1.36)	Merritt 2008 1.13 (0.92 - 1.38)	
Mills 2004 1.37 (1.02 - 1.85)	Mills 2004 1.37 (1.02 - 1.85)	Mills 2004 1.37 (1.02 - 1.85)
	Moorman 2009 1.37 (1.05 - 1.8)	
Ness 2000 1.50 (1.10 - 2.02)	Ness 2000 1.50 (1.10 - 2.00)	Ness 2000 1.50 (1.10 - 2.00)
Purdie 1995 1.27 (1.04 - 1.54)	Purdie 1995 1.27 (1.04 - 1.54)	Purdie 1995 1.27 (1.04 - 1.54)
Rosenblatt 1992 1.70 (0.72 - 4.01)	Rosenblatt 1992 1.70 (0.70 - 3.90)	Rosenblatt 1992 1.70 (0.70 - 3.90)
Rosenblatt 2011 1.27 (0.97 - 1.66)	Rosenblatt 2011 1.13 (0.93 - 1.36)	
Schildkraut 2016 1.44 (1.11 - 1.86)	Schildkraut 2016 1.44 (1.11 - 1.86)	Schildkraut 2016 A 1.44 (1.11 - 1.86)
		Schildkraut 2016 B 1.19 (0.87 - 1.63)
Shushan 1996 2.00 (1.11 - 3.60)		Shushan 1996 1.97 (1.06 - 3.66)

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Penninkilampi 2018 Study / RR(95%CI)	Berge 2018 Study / RR(95%CI)	Siemiatycki 2018 Study / RR(95%CI)
<i>Tzonou 1993</i> 1.05 (0.28 - 3.96)	<i>Tzonou 1993</i> 1.05 (0.28 - 3.98)	Terry 2013 1.24 (1.15 - 1.33)
Whittemore 1988 1.40 (0.98 - 2.00)	<i>Whittemore 1988</i> 1.36 (0.91 - 2.04)	<i>Tzonou 1993</i> 1.05 (0.28 - 3.98)
Wong 1999 0.92 (0.24 - 3.57)	<i>Wong 1999</i> 1.00 (0.80 - 1.30)	<i>Whittemore 1988</i> 1.36 (0.91 - 2.04)
Wu 2015 1.32 (1.14 - 1.52)	<i>Wu 2015</i> 1.46 (1.27 - 1.69)	<i>Wong 1999</i> 1.00 (0.80 - 1.30)
		<i>Wu 2015</i> 1.46 (1.27 - 1.69)

- * When two or three of the meta-analyses extracted the identical results from the source paper, it is indicated with italic characters.

15. Appendix C

Examples of historic discoveries made on the basis of empirical observation of an association, without the existence of a validated biological mechanism of action.

- Jenner (18th century) discovered that smallpox could be prevented by “vaccinating” people. This was based on observation of the effect of exposure to cowpox. He had no idea about viruses or the biology of smallpox. He only knew that the “association” he observed between vaccination and the prevention of smallpox was so strong as to convince him it was causal. Millions of lives were saved as a result.
- Snow (19th century) discovered that cholera was caused by something in the water supply. He did not know what the pathogen was or how it produced the disease, but he showed with sufficient epidemiologic proof that drinking water from a polluted source produced much higher rates than drinking water from a clean source. Despite the ignorance of biological mechanisms, the public health authorities acted on his findings and thereby greatly reduced the incidence of cholera.
- Rheumatic fever and rheumatic heart disease were quite common causes of disease and death, striking relatively young people. For many decades it was recognized that there was an association between infection with the streptococcus bacterium and rheumatic heart disease, but it was not understood how the bacterium could have such an effect. The lack of understanding of the biological mechanisms did not get in the way of prevention of rheumatic heart disease by preventing and treating streptococcus infection.
- In the 1930’s and 1940’s, it was noticed that communities with high natural levels of fluoride in the water had much lower levels of dental caries than communities with low fluoride levels. Additional observational research confirmed the clear causal relationship and this led to extensive use of fluoride in various ways to reduce dental disease. But, all this occurred

before the mechanisms by which fluoride acted on teeth were understood. And, indeed the mechanisms are still not fully understood.

- In the late 1940's and early 1950's, evidence was accumulating that cigarette smokers had higher rates of lung cancer than non-smokers. This "association" was ridiculed at the time, among other reasons, because there was no proven biological mechanism. Attempts to replicate smoking-related lung cancer incidence in laboratory animals were largely unsuccessful. Nor was there a deep understanding of the cellular processes that allow the inhalation of cigarette smoke to culminate in a tumor. Scores of studies later and many decades later, the outlines of a credible biological mechanism began to emerge. The absence of a proven biological mechanism did not hinder the US Surgeon General and other national bodies from concluding that there was a causal link as early as the 1960's.

- Many chemicals have been found to be carcinogenic as a result of epidemiologic studies among workers. Examples of these are asbestos, silica, nickel compounds, chromium compounds, benzene, and others. Some of these discoveries go back to the first half of the 20th century, and, for most of them, many decades passed between the time they were recognized as carcinogens, on the basis of epidemiologic associations, and the elaboration of credible mechanisms of how they induce cancer. (Siemiatycki 2015) Most known carcinogens were first discovered empirically by medical doctors or epidemiologists, usually as part of large data collection activities or just plain astute observation on the part of medical doctors.

16. References

Bibliography Part A: Documents available in the Public Domain

Anderson E, P Sheehan, R Kalmes, J Griffin (2017). Assessment of health risk from historical use of cosmetic talcum powder, *Risk Analysis* 37(5):918-929.

Aune D, Giovannucci E, Boffetta P, Fadnes L, Keum N, Norat T, Greenwood D, Riboli E, Vatten L, Tonstad S (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies, *International Journal of Epidemiology* 43(3):1029-1056.

Begg, March (2018). Cause and association: missing the forest for the trees. *American Journal of Public Health (AJPH)* Vol 108, No.5.

Berge, Mundt, Luu and Boffetta (2017, published 2018). Genital use of talc and risk of ovarian cancer: a meta-analysis. *The European Journal of Cancer Prevention* 27(3): 248-257.

Booth, M., V. Beral and P. Smith (1989). Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer* 60(4): 592-598.

Blount A. (1991). Amphibole content of cosmetic and pharmaceutical talcs, *Environmental Health Perspectives*, 94:225-230.

Boffetta, Hayes, Satori, et al. (2016) Mouthwash use and cancer of the head and neck: a pooled analysis from the International Head and Neck Cancer Epidemiology Consortium. *The European Journal of Cancer Prevention* 25(4): 344-8.

Boorman G, J Seely (1995). The lack of ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice, *Regulatory Toxicology and Pharmacology* 21:242-243.

Booth, M., V. Beral and P. Smith (1989). Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer* 60(4): 592-598.

Bunderson-Schelvan M, J Pfau, R Crouch, A Holian (2011). Nonpulmonary outcomes of asbestos exposure, *Journal of Toxicology and Environmental Health, Part B* 14:122-152.

- Buz'Zard, Lau (2007). Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research Journal* 21(6):579-86.
- Camargo M, L Stayner, K Straif, M Reina, U Al-Alem, P Demers, P Landrigan (2011). Occupational exposure to asbestos and ovarian cancer: a meta-analysis, *Environ Health Perspect* 119:1211–1217.
- Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs, Jr DR, Liu K (2003). Cardiorespiratory Fitness in Young Adulthood and the Development of Cardiovascular Disease Risk Factors. *JAMA*, 290(23):3092–3100.
- Carr CJ (1995). Talc: Consumer Uses and Health Perspectives, *Regulatory Toxicology and Pharmacology* 21:211-215.
- Cerhan, J., Z. Fredericksen, A. Wang, T. Habermann, N. Kay, W. Macon, J. Cunningham, T. Shanafelt, S. Answell, T. Call, T. Witzig, S. Slager, M. Liebow (2011). Design and validity of a clinic-based case-control study on the molecular epidemiology of lymphoma. *International Journal of Molecular Epidemiology and Genetics* 2(2): 95-113.
- Chang, S. and H. A. Risch (1997). Perineal talc exposure and risk of ovarian carcinoma. *Cancer* 79(12): 2396-2401.
- Chen, Y., P. C. Wu, J. H. Lang, W. J. Ge, P. Hartge and L. A. Brinton (1992). Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology* 21(1): 23-29.
- CIR (2013). *Safety Assessment of Talc as Used in Cosmetics*. Washington, D.C., CIR (Cosmetic Ingredient Review).
- Cook, L. S., M. L. Kamb and N. S. Weiss (1997). Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology* 145(5): 459-465.
- Coussens, L. M. and Z. Werb (2002). Inflammation and cancer. *Nature* 420(6917): 860-867.
- Cralley L, M Key, D Groth, W Lainhart, R Ligo. (1968). Fibrous and mineral content of cosmetic talcum products, *American Industrial Hygiene Association Journal*, 29(4):350-354.

- Cramer, D. W. (2015). Opinion on the Relationship between Ovarian Cancer and Cosmetic Talc Powder Use: Causality and Relevance to the Case of Michael Blaes OBO Shawn Blaes. Civil Action Number 4:14-cv-00213. Unpublished report.
- Cramer, D. W., R. F. Liberman, L. Titus-Ernstoff, W. R. Welch, E. R. Greenberg, J. A. Baron and B. L. Harlow (1999). Genital talc exposure and risk of ovarian cancer. *International Journal of Cancer* 81(3): 351-356.
- Cramer, D. W., L. Titus-Ernstoff, J. R. McKolanis, W. R. Welch, A. F. Vitonis, R. S. Berkowitz and O. J. Finn (2005). Conditions Associated with Antibodies Against the Tumor-Associated Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer. *Cancer Epidemiology, Biomarkers & Prevention* 14(5): 1125-1131.
- Cramer, D. W., A. F. Vitonis, K. L. Terry, W. R. Welch and L. J. Titus (2016). The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. *Epidemiology* 27(3): 334-346.
- Cramer, D. W., W. R. Welch, R. S. Berkowitz and J. J. Godleski (2007). Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstetrics & Gynecology* 110(2 Part 2): 498-501.
- Cramer, D. W., W. R. Welch, R. E. Scully and C. A. Wojciechowski (1982). Ovarian cancer and talc: a case-control study. *Cancer* 50(2): 372-376.
- Cramer, D. W. and H. Xu (1995). Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Annals of Epidemiology* 5(4): 310-314.
- Current Intelligence Bulletin 62 (Rev/ 4/2011)- Asbestos fibers and other elongate mineral particles: state of the science and roadmap for research. *National Institute for Occupational Safety and Health (NIOSH)* DHHS (NIOSH) Publication No. 2011-159
- Dement, Shuler, Zumwalde (1972). "Fiber exposure during use of baby powders" *National Institute for Occupational Safety and Health*, IWS 36-6: 1-13.
- Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on British male doctors, *British Medical Journal*, 328(7455):1519.

- Egli G, M. Newton (1961). The transport of carbon particles in the human female reproductive tract, *Fertility and Sterility* 12(April):151-55.
- Eltabbakh, G. H., M. S. Piver, N. Natarajan and C. J. Mettlin (1998). Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. *Obstetrics & Gynecology* 91(2): 254-259.
- Fedak K, A. Bernal, Z Capshaw, S Gross (2015). Applying the Bradford Hill criteria in the 21st Century: How data integration has changed causal inference in molecular epidemiology, *Emerging Themes in Epidemiology* 12(14)
<https://doi.org/10.1186/s12982-015-0037-14>
- Federal Judicial Center and National Research Council of the National Academies (2011). *Reference Manual on Scientific Evidence, Third Edition*. Washington, D.C., The National Academies Press.
- Federal Register (2016). Banned Devices; Powdered Surgeon's Gloves; Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon Glove – powdered gloves. *Food and Drug Administration* 81FR 91722.
- Fletcher N, J Belotte, M Saed, I Memaj, M Diamond, R Morris, G Saed (2016). Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer, *Free Radical Biology and Medicine*, 102:122-132.
- Fletcher N, I Memaj, G Saed (2018). Talcum powder enhances oxidative stress in ovarian cancer cells – Abstract, *Reproductive Sciences*, 25(Supp. 1):214A.
- Fletcher N, G. Saed (2018). Talcum powder enhances cancer antigen 125 levels in ovarian cancer cells – Abstract, *Society for Reproductive Investigation 65th Annual Scientific Meeting*, LB-044.
- Fiume, M., I. Boyer, W. Bergfeld, D. Belsito, R. Hill, C. Klaassen, D. Liebler, J. Marks, Jr., R. Shank. T. Slaga, P. Synder, F.A. Andersen (2015). Safety Assessment of Talc as Used in Cosmetics. *International Journal of Toxicology* 34(Supplement I): 66S-129S.
- Folkins A, E Jarboe, J Hecht, M Muto and C Crum (2018). "Chapter 24 – Assessing pelvic epithelial cancer risk and intercepting early malignancy." In *Diagnostic Gynecologic*

- and Obstetric Pathology (Third Edition)*, 844-64. Philadelphia: Content Repository Only! <https://doi.org/10.1016/B978-0-323-44732-4.00024-8>.
- Gandini S, Sera F, Cattaruzza MS, et al (2004). Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *European Journal of Cancer* 41:45-60.
- Gates, M. A., B. A. Rosner, J. L. Hecht and S. S. Tworoger (2010). Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology* 171(1): 45-53.
- Gates, M. A., S. S. Tworoger, K. L. Terry, I. De Vivo, D. J. Hunter, S. E. Hankinson and D. W. Cramer (2009). Breast cancer susceptibility alleles and ovarian cancer risk in 2 study populations. *International Journal of Cancer* 124(3): 729-733.
- Gates, M. A., S. S. Tworoger, K. L. Terry, L. Titus-Ernstoff, B. Rosner, I. De Vivo, D. W. Cramer and S. E. Hankinson (2008). Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiology, Biomarkers & Prevention* 17(9): 2436-2444.
- Gertig, D. M., D. J. Hunter, D. W. Cramer, G. A. Colditz, F. E. Speizer, W. C. Willett and S. E. Hankinson (2000). Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute* 92(3): 249-252.
- Gloyne S (1935). Two cases of squamous carcinoma of the lung occurring in asbestosis, *Tubercle* (17)1: 5-10.
- Godard, B., W. D. Foulkes, D. Provencher, J. S. Brunet, P. N. Tonin, A. M. Mes-Masson, S. A. Narod and P. Ghadirian (1998). Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *American Journal of Obstetrics & Gynecology* 179(2): 403-410.
- Gonzalez, N. L., K. M. O'Brien, A. A. D'Aloisio, D. P. Sandler and C. R. Weinberg (2016). Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiology* 20: 20.
- Goodman, M. T., G. Lurie, P. J. Thompson, K. E. McDuffie and M. E. Carney (2008). Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. *Endocrine-Related Cancer* 15(4): 1055-1060.

- Gordon R, S Fitzgerald, and J Millette (2014). Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women, *International Journal of Occupational and Environmental Health*, 20(4): 318-332.
- Green, A., D. Purdie, C. Bain, V. Siskind, P. Russell, M. Quinn and B. Ward (1997). Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *International Journal of Cancer* 71(6): 948-951.
- Grivennikov, S. I., F. R. Greten and M. Karin (2010). Immunity, inflammation, and cancer. *Cell* 140(6): 883-899.
- Gross, A. J. and P. H. Berg (1995). A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. *Journal of Exposure Analysis & Environmental Epidemiology* 5(2): 181-195.
- Hamilton T, H Fox H, C Buckley CH, W Henderson, K Griffiths. Effects of talc on the rat ovary. *British journal of experimental pathology*. 1984;65(1):101-6Hamra GB, Guha N, Cohen A, et al (2014). Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis, *Environ Health Perspect* 122:906-911.
- Hankinson, S. E., D. J. Hunter, G. A. Colditz, W. C. Willett, M. J. Stampfer, B. Rosner, C. H. Hennekens and F. E. Speizer (1993). Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. *JAMA* 270(23): 2813-2818.
- Harlow, B. L., D. W. Cramer, D. A. Bell and W. R. Welch (1992). Perineal exposure to talc and ovarian cancer risk. *Obstetrics & Gynecology* 80(1): 19-26.
- Harlow, B. L. and N. S. Weiss (1989). A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *American Journal of Epidemiology* 130(2): 390-394.
- Harper A, G Saed (2018). Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes - Abstract, *Society of Gynecologic Oncology*, in press.
- Hartge, P., R. Hoover, L. P. Leshner and L. McGowan (1983). Talc and ovarian cancer. *JAMA* 250(14): 1844.

Heath, David. (2016) "Philip Morris uses chemical industry consultants to perpetuate 'light cigarette' myth" – <https://www.publicintegrity.org/2016/05/04/19618/philip-morris-uses-chemical-industry-consultants-perpetuate-light-cigarette-myth>

Heller, D. S., C. Westhoff, R. E. Gordon and N. Katz (1996). The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *American Journal of Obstetrics & Gynecology* 174(5): 1507-1510.

Hernan (2018). The C-Word: scientific euphemisms do not improve causal inference from observational data. *The American Journal of Public Health (AJPH)* Vol 108, No.5: 616-619

Henderson, W. J., T. C. Hamilton and K. Griffiths (1979). Talc in normal and malignant ovarian tissue. *Lancet* 1(8114): 499.

Henderson, W. J., C. A. Joslin, A. C. Turnbull and K. Griffiths (1971). Talc and carcinoma of the ovary and cervix. *Journal of Obstetrics & Gynaecology British Commonwealth* 78(3): 266-272.

Henderson, W.J., T.C. Hamilton, M.S. Baylis, C.G. Pierrepont, K. Griffiths (1986). The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat, *Environmental Research* 40:247-250.

Hill, A. B. (1965). The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 58: 295-300.

Houghton, S. C., K. W. Reeves, S. E. Hankinson, L. Crawford, D. Lane, J. Wactawski-Wende, C. A. Thomson, J. K. Ockene and S. R. Sturgeon (2014). Perineal powder use and risk of ovarian cancer. *Journal of the National Cancer Institute* 106(9).

Huncharek, M., J. F. Geschwind and B. Kupelnick (2003). Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Research* 23(2C): 1955-1960.

Huncharek, M. and J. Muscat (2011). Perineal talc use and ovarian cancer risk: a case study of scientific standards in environmental epidemiology. *European Journal of Cancer Prevention* 20(6): 501-507.

Huncharek, M., J. Muscat, A. Onitilo and B. Kupelnick (2007). Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies. *European Journal of Cancer Prevention* 16(5): 422-429.

IARC Monograph 1-42 (1972-1987) - Evaluation of the Carcinogenic risk of chemicals to humans. *International Agency for Research on Cancer/World Health Organization*, WHO Press.

IARC (1996). *Mechanisms of mineral fibre carcinogenesis. Publication No, 140*. Kane AB, Boffeta P, Saracci R, Wilbourn JD, *IARC Scientific*

IARC (2010). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 93. Carbon black, titanium dioxide, and talc*. Lyon, IARC (International Agency for Research on Cancer).

IARC (2011). *IARC Monographs on Design and validity of a clinic base control-study on the molecular epidemiology of lymphoma, Vol. 93*. James R. Cerhan, Zachary S. Fredericksen, Alice H Wang, Thomas M. Habermann, Neil E. Kay, William R. Macon, Julie M. Cunningham, Tait D. Shanfelt, Stephen M. Answell, Thimothy G. Call, Thomas E. Witzig, Susan L. Slager, Mark Liebow, IARC (International Agency for Research on Cancer).

IARC - Monograph Vol. 100C (2012)- Arsenic, Metals Fibres, and Dusts: A review of human carcinogens. Lyon, *International Agency for Research on Cancer/World Health Organization*.

Ioannidis J (2005). Why most published research findings are false, *PLoS Med*, 2(8):e124.

Ioannidis J (2015). Exposure-wide epidemiology: revisiting Bradford Hill, *Statistics in Medicine*

Jordan, S. J., A. C. Green, D. C. Whiteman, P. M. Webb and Australian Ovarian Cancer Study Group (2007). Risk factors for benign serous and mucinous epithelial ovarian tumors. *Obstetrics & Gynecology* 109(3): 647-654.

Karami S, Lan Q, Rothman N, et al (2012). Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. *Occupational and Environmental Medicine* 69:858-867.

Kasper CS, Chandler PJ, Jr. Possible morbidity in women from talc on condoms. *JAMA*. 1995;273(11):846-7.

Khalade A, Jaakkola MS, Pukkala E, Jaakkola JJ (2010). Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environmental Health* 9(31):1-8.

Kim S, Ko Y, Lee HJ, Lim J (2018). Menopausal hormone therapy and the risk of breast cancer by histological type and race: a meta-analysis of randomized controlled trials and cohort studies. *Breast Cancer Research and Treatment* 170(3):667-675.

Krause J (1977). Mineralogical characterization of cosmetic talc products, *Journal of Toxicology and Environmental Health* 2(5):1223-1226. Kurta, M. L., K. B. Moysich, J. L. Weissfeld, A. O. Youk, C. H. Bunker, R. P. Edwards, F. Modugno, R. B. Ness and B. Diergaarde (2012). Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiology, Biomarkers & Prevention* 21(8): 1282-1292.

Langseth, H., S. E. Hankinson, J. Siemiatycki and E. Weiderpass (2008). Perineal use of talc and risk of ovarian cancer. *Journal of Epidemiology & Community Health* 62(4): 358-360.

Langseth, H. and K. Kjaerheim (2004). Ovarian cancer and occupational exposure among pulp and paper employees in Norway. *Scandinavian Journal of Work, Environment & Health* 30(5): 356-361.

Last, J. M. (2001). *A Dictionary of Epidemiology, Fourth Edition*. Oxford, Oxford University Press.

Levin. "Baby powder battles: Johnson & Johnson internal documents reveal asbestos worries" - <https://www.fairwarning.org/2018/01/talc-documents-reveal/print>

- Licaj, Jacobsen, Selmer et al. (2017). Smoking and risk of ovarian cancer by histological subtypes: an analysis among 300,000 Norwegian women. *British Journal of Cancer* 116(2): 270-276
- Lo-Ciganic, W. H., J. C. Zgibor, C. H. Bunker, K. B. Moysich, R. P. Edwards and R. B. Ness (2012). Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology* 23(2): 311-319.
- Lockey J (1981). Nonasbestos fibrous minerals, *Clinics in Chest Medicine* 2(2):203-218.
- Lundin, Dossus, Clendenen, Krogh, Grankvist, Wulff, Sieri, Arlsan, Lenner, Berrino, Hallmans, Zeleniuch-Jacquotte, Toniolo, Lukanova (2009). C-reactive protein and ovarian cancer: a prospective study nested in three cohorts (Sweden, USA, Italy). *Cancer Causes & Control: CCC* 20(7):1151-1159.
- Lunet, N., and A. Azevedo (2009). Letter to the Editor: On the comparability of population-based and hospital-based case-control studies. *Gaceta Sanitaria* 23(6): 564-567.
- Mahjub H, Sadri G (2006). Meta-analysis of case-referent studies of specific environmental or occupational pollutants on lung cancer. *Indian Journal of Cancer* 43(4):169-173.
- Mallen, Townsend, Tworoger (2018). Risk factors for ovarian carcinoma. *Hematology/Oncology Clinics of North America*. 32(6):891-902.
- Masi, A. (1965). Potential uses and limitations of hospital data in epidemiologic research. *American Journal of Public Health* 55(5): 658-667.
- Mattenklott (2007). Asbestos in talc powders and soapstone – the present state . *Staub, Reinhaltung der Luft Journal* 67(7):287-292.
- Mayer D, C Kasper, P Chandler (1995). To the Editor: Talc and Condoms and reply, *JAMA* 274(16):1269.
- Merritt, M. A., A. C. Green, C. M. Nagle, P. M. Webb, Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group (2008). Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer* 122(1): 170-176.

- Mills, P. K., D. G. Riordan, R. D. Cress and H. A. Young (2004). Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *International Journal of Cancer* 112(3): 458-464.
- Miserocchi G, G Sancini, F Mantegazza, G Chiappino (2008). Translocation pathways for inhaled asbestos fibers, *Environmental Health* 7:4 doi: 10.1186/1476-069X-7-4.
- Moller P, P Danielsen, K Jantsen, M Roursgaard & S Loft (2013). Oxidatively damaged DNA in animals exposed to particles, *Critical Reviews in Toxicology*, 43:2, 96-118.
- Moller, Jacobsen et al (2010). Role of oxidative damage in toxicity of particulates, *Free Radical Researchm* 44:1, 1-46.
- Moon M, J Park, B Choi, S Park, D Kim, Y Chung, N Hisanaga, I Yu (2011). Risk assessment of baby powder exposure through inhalation. *Official Journal of Korean Society of Toxicology*, 27(3): 137-147.
- Moorman, P. G., R. T. Palmieri, L. Akushevich, A. Berchuck and J. M. Schildkraut (2009). Ovarian cancer risk factors in African-American and white women. *American Journal of Epidemiology* 170(5): 598-606.
- Muscat J.E., Huncharek M (2008). Perineal Talc Use and Ovarian Cancer: A Critical Review. *European J Cancer Prevention* 17:139-146.
- Narod S (2016). Talc and ovarian cancer. *Gynecologic Oncology* 141(3):410-12.
<https://doi.org/10.1016/j.ygyno.2016.04.011>.
- Ness, R. B. and C. Cottreau (1999). Possible role of ovarian epithelial inflammation in ovarian cancer. *Journal of the National Cancer Institute* 91(17): 1459-1467.
- Ness, R. B., J. A. Grisso, C. Cottreau, J. Klapper, R. Vergona, J. E. Wheeler, M. Morgan and J. J. Schlesselman (2000). Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* 11(2): 111-117.
- Ness, Roberta (2015)– Does talc exposure cause ovarian cancer?:IGCS-0015 Ovarian Cancer. *International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society*, 25 Suppl. 1:51

Neupane, B., S. Walter, P. Krueger, M. Loeb (2010). Community controls were preferred to hospital controls in a case-control study where the cases are derived from the hospital. *Journal of Clinical Epidemiology* 63(8): 926-931.

Paoletti, Caiazza, et al (1984). Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. *Regulatory Toxicology and Pharmacology* 4(3):222-35.

Park, Schildkraut, et al. (2018) Benign gynecologic conditions are associated with ovarian cancer risk in African-American women: a case-control study. *Cancer Causes & Control* Vol. 29, Issue 11, pp 1081-1091.

Peeples, Lynne (2014) "Hidden source of industry influence threatens toxic chemical regulations" – https://huffingtonpost.com/2014/09/18/industry-toxic-chemicals-funding-conflicts-of-interest_n_5837968.html

Pennikilampi R, G Eslick (2018). Perineal talc use and ovarian cancer: a systematic review and meta-analysis, *Epidemiology*, 29:41-49.

Petitti, D. B. (2000). *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis*. New York, Oxford University Press.

Pike, M. C., C. L. Pearce, R. Peters, W. Cozen, P. Wan and A. H. Wu (2004). Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertility & Sterility* 82(1): 186-195.

Purdie, D., A. Green, C. Bain, V. Siskind, B. Ward, N. Hacker, M. Quinn, G. Wright, P. Russell and B. Susil (1995). Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *International Journal of Cancer* 62(6): 678-684.

Reid, Permuth, Sellers (2017). *Epidemiology of ovarian cancer: a review. Cancer Biology and Medicine* 14(1): 9-32.

VL Roggli, PC Pratt (1983). Numbers of asbestos bodies on iron-stained tissue sections in relation to asbestos body counts in lung tissue digest. *Human Pathology Journal* 14(4): 355-61.

VL Roggli, PC Pratt, AR Brody(1986). Asbestos content of lung tissue in asbestos associated diseases: a study of 110 cases. *British Journal of Industrial Medicine* 43(1): 18-28.

Rohl A (1974). Asbestos in Talc, *Environmental Health Perspectives*, 9:129-132.

Rohl A, A. Langer, J. Selikoff, A. Tordini, R. Klimentidis (1976). Consumer talcums and powders: mineral and chemical characterization. *Journal of Toxicology and Environmental Health* 2(2):255-84.

Rosenblatt, K. A., W. A. Mathews, J. R. Daling, L. F. Voigt and K. Malone (1998). Characteristics of women who use perineal powders. *Obstetrics & Gynecology* 92(5): 753-756.

Rosenblatt, K. A., M. Szklo and N. B. Rosenshein (1992). Mineral fiber exposure and the development of ovarian cancer. *Gynecologic Oncology* 45(1): 20-25.

Rosenblatt, K. A., N. S. Weiss, K. L. Cushing-Haugen, K. G. Wicklund and M. A. Rossing (2011). Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control* 22(5): 737-742.

Ross, Malcom (1974)Geology, asbestos and health. *The National Institute of Environmental Health Sciences* 9:123-124

Rothan, Pastides, Samet (2000). Interpretation of epidemiologic studies on Talc and Ovarian Cancer.

Rothman, K. J. and S. Greenland (1998). *Modern Epidemiology, Second Edition*. Philadelphia, Lippincott-Raven Publishers.

Rothman, K., Greenland, S., & Lash, TL. (2008). *Modern Epidemiology, 3rd Edition*. Philadelphia, PA: Lippincott Williams & Wilkins.

Ruano-Ravina, A., M. Perez-Rios, J. Barros-Dios (2008). Population-based versus hospital-based controls: are they comparable? *Gaceta Sanitaria* 22(6): 609-613.

Saed G, R Morris, N Fletcher (2018). *New insights into the pathogenesis of ovarian cancer-oxidative stress, Ovarian Cancer – From Pathogenesis to Treatment*, Ch. 4, 83-110, IntechOpen.

Saed G, M Diamond, N Fletcher (2017). Updates of the role of oxidative stress in the pathogenesis of ovarian cancer, *Gynecologic Oncology*, 145:595-602.

Schildkraut, J. M., S. E. Abbott, A. J. Alberg, E. V. Bandera, J. S. Barnholtz-Sloan, M. L. Bondy, M. L. Cote, E. Funkhouser, L. C. Peres, E. S. Peters, A. G. Schwartz, P. Terry, S. Crankshaw, F. Camacho, F. Wang and P. G. Moorman (2016). Association between Body Powder Use and Ovarian Cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology, Biomarkers & Prevention* 12: 12.

Shukla A, M MacPherson, J Hillegass, M Ramos-Nino, V Alexeeva, P Vacek, J Bond, H Pass, C Steele, B Mossman (2009). Alterations in gene expression in human mesothelial cells correlated with mineral pathogenicity, *American Journal of Respiratory Cell and Molecular Biology*, 41:114-123.

Shushan, A., O. Paltiel, J. Iscovich, U. Elchalal, T. Peretz and J. G. Schenker (1996). Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertility & Sterility* 65(1): 13-18.

Siemiatycki J. Historical overview of occupational cancer research and control. In Occupational Cancers. Eds S Anttila, P Boffetta, K Straif. Springer Press: 1-20, 2014.

Sjosten A, H Ellis, G Edelstam (2004). Retrograde migration of glove powder in the human female genital tract, *Human Reproduction* 19(4):991-995.

Smith, Guyton, Gibbons, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environmental Health Perspectives* 124(6):713-21

Steiling W, Almeida JF, Assaf Vandecasteele H, Gilpin S, Kawamoto T, O'Keeffe L, Pappa G, Rettinger K, Rothe H, Bowden AM (2018) Principles for the safety evaluation of cosmetic powders, *Toxicology Letters*, 297, 8-18.

Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Guha N, Freeman C, Galichet L, Coglian V; WHO International Agency for Research on Cancer Monograph Working Group (2009). A review of human carcinogens - Part C: metals, arsenic, dusts and fibres, *Lancet Oncology* 10(5):453-454. Suzuki Y, N

- Kohyama (1991). Translocation of inhaled asbestos fibers from the lung to other tissue, *American Journal of Industrial Medicine* 19(6):701-704.
- Terry, K. L., S. Karageorgi, Y. B. Shvetsov, M. A. Merritt, G. Lurie, P. J. Thompson, M. E. Carney, R. P. Weber, L. Akushevich, W. H. Lo-Ciganic, K. Cushing-Haugen, W. Sieh, K. Moysich, J. A. Doherty, C. M. Nagle, A. Berchuck, C. L. Pearce, M. Pike, R. B. Ness, P. M. Webb, M. A. Rossing, J. Schildkraut, H. Risch and M. T. Goodman (2013). Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls. *Cancer Prevention Research* 6(8): 811-821.
- Trabert G, E Poole, E White, K Visvanathan, H Adami, G Anderson, T Brasky et al. (2018). Analgesic use and ovarian cancer risk: an analysis in the Ovarian Cancer Cohort Consortium, *Journal of the National Cancer Institute* 111(2)
<https://doi.org/10.1093/jnci/djy100>.
- Tung, Goodman, Wu, et al. (2005) Reproductive factors and epithelial ovarian cancer risk by histologic type: a multi-ethnic case-control study. *American Journal of Epidemiology* 161(4):321-9.
- Tung, Wilkes, Wu, et al. (2003). Effect of anovulation factors on pre-and postmenopausal ovarian cancer risk: revisiting the incessant ovulation hypothesis. *American Journal of Epidemiology* 158(7): 629-38
- Tzonou, A., A. Polychronopoulou, C. C. Hsieh, A. Rebelakos, A. Karakatsani and D. Trichopoulos (1993). Hair Dyes, Analgesics, Tranquilizers and Perineal Talc Application as Risk Factors for Ovarian Cancer. *International Journal of Cancer* 55(3): 408-410.
- U.S. Department of Health, E., and Welfare, (1964). *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington, D.C., U.S. Department of Health, Education, and Welfare.
- Van Gosen B, H Lowers, S Sutley, and C. Gent (2004). Using the geologic setting of talc deposits as an indicator of amphibole asbestos content, *Environmental Geology*, 45 (7):920-939.

Venter, P. F. and M. Iturralde (1979). Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *South African Medical Journal* 55(23): 917-919.

Virta, Robert L. (1985). The phrase relationship of talc and amphiboles in a fibrous talc sample. Vol. 8923 of the *U.S. Dept. of the Interior, Bureau of Mines– Science*.

Weed, D. L. (2000). Epidemiologic evidence and causal inference. *Hematological & Oncological Clinics of North America* 14(4): 797-807, viii.

Wehner A, A Hall, R Weller, E Lepel, R Schirmer (1985). Do particles translocate from the vagina to the oviducts and beyond? *Fd Chem. Toxic.* 23(3) :367-372.

Werner I (1982). Presence of asbestos in talc samples, *Atenschutzinformationen*, 21:5-7.

Wentzensen, N. and S. Wacholder (2014). Talc use and ovarian cancer: epidemiology between a rock and a hard place. *Journal of the National Cancer Institute* 106(9).

Whittemore, A. S., M. L. Wu, R. S. Paffenbarger, Jr., D. L. Sarles, J. B. Kampert, S. Grosser, D. L. Jung, S. Ballon and M. Hendrickson (1988). Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology* 128(6): 1228-1240.

Whysner, J. and M. Mohan (2000). Perineal application of talc and cornstarch powders: evaluation of ovarian cancer risk. *American Journal of Obstetrics & Gynecology* 182(3): 720-724.

Wong, C., R. E. Hempling, M. S. Piver, N. Natarajan and C. J. Mettlin (1999). Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstetrics & Gynecology* 93(3): 372-376.

Wu, A. H., C. L. Pearce, et al. (2009). Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer* 124(6): 1409-1415.

Wu AH, CL Pearce, CC Tseng, MC Pike (2015). African-Americans and Hispanics remain at lower risk of ovarian cancer than non-hispanic whites after considering nongenetic

risk factors and oophorectomy rates, *Cancer Epidemiol Biomarkers Prev* 24(7):1094-1100.

Wu S, W Zhu, P Thompson, Y Hannun (2018) Evaluating intrinsic and non-intrinsic cancer risk factors, *Nature Communications* 9(1):3490.

Zazenski R, W Ashton, D Briggs, M Chudkowski, J Kelse, L MacEachern, E McCarthy, M Nordhauser, M Roddy, N Teetsel, A Wells, S Gettings (1995). Talc: Occurrence, characterization and consumer applications, *Regulatory Toxicology and Pharmacology* 21:218-229.

Zhang Z-L, Sun J, Dong J-Y, et al (2012). Residential Radon and Lung Cancer Risk: An Updated Meta-analysis of Case-control Studies. *Asian Pac J Cancer Prev* 13:2459-2465.

Bibliography – Part B: Documents not available in the Public Domain

IMERYS044612

IMERYS049952-56

IMERYS051371-72

IMERYS051442

IMERYS089960

IMERYS091279-80

IMERYS111220

IMERYS126092-97

IMERYS138505-11

IMERYS179122-23

IMERYS210136-37

IMERYS219720-22

IMERYS239864

IMERYS2419940-04

IMERYS242050

IMERYS274896

IMERYS284935-37

IMERYS288001-04

IMERYS288590-91

IMERYS303801

IMERYS322241-42

IMERYS342524-25

IMERYS422289-90

IMERYS442232-33

IMERYS500801

IMERYS-A_0001304-09

IMERYS-A_0011817

IMERYS-A_0011964-65

IMERYS-A_0021921-29

IMERYS-A_0024367

IMERYS-MDL-AB_0005560-86

JNJ000000119-22

JNJ000000523-36

JNJ000000636-38

JNJ000000697

JNJ000000704

JNJ000000935-36

JNJ000003914-15

JNJ000003969-72

JNJ000003987-95

JNJ000004113-24

JNJ000004152-56

JNJ000004183

JNJ000004225-30

JNJ000004518-21

JNJ000004541-42

JNJ000004545-46

JNJ000004641-42

JNJ000004712-16

JNJ000006201-02

JNJ000008945-9277

JNJ000010808

JNJ000011704-08

JNJ000013664-65

JNJ000015750-52

JNJ000015753-54

JNJ000015770-72

JNJ000016645-46

JNJ000020397

JNJ00002073337

JNJ000021035

JNJ000021093-94

JNJ000022040-42

JNJ000023355-56

JNJ000024462-63

JNJ000024495-500

JNJ000024568

JNJ000251888-90

JNJ000261010-27

JNJ000029640-41

JNJ000035173-231

JNJ000036440-42

JNJ000040596-97

JNJ000058760-64

JNJ000065616-19

JNJ000075792-94

JNJ000085127-39

JNJ000085448-60

JNJ000087166-230

JNJ000092918-20

JNJ000093405

JNJ000093406-97

JNJ000175138

JNJ000221838-49

JNJ000223499

JNJ000224655-93

JNJ000238435-39

JNJ000239388

JNJ000232996-3002

JNJ000246437

JNJ000248615-16

JNJ000251888-90

JNJ000257999

JNJ000261010-27

JNJ000260833-35

JNJ000278435-39

JNJ000290508-28

JNJ000298951-52

JNJ000326106-25

JNJ000342731-34

JNJ000346841

JNJ000348778-80

JNJ000367403-56

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JNJ000375563

JNJ000375919

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JNJ000381975-76

JNJ000383680-82

JNJ000383898

JNJ000384724-28

JNJ000384731-37

JNJ000384773

JNJ000385452

JNJ000388419

JNJ000389973-74

JNJ000391191

JNJ000391530

JNJ000394463-JNJ000394467

JNJ000404446-47

JNJ000404486-88

JNJ000405501-53

JNJ000411712-15

JNJ000418480

JNJ000457407-10

JNJ000637879-81

JNJ000526231-6676

J&J-0007797

JNJAZ55_000000904-948

JNJAZ55_000003357

JNJAZ55_000005743-48

JNJAZ55_000005957-66

JMJAZ55_00006089-091

JANJAZ55_000008177-78

JNJAZ55_000008893-8902

JNJAZ55_000012423-30

JNJAZ55_000015127-286

JNJMX68_000003728-29

JNJMX68_000004646-47

JNJMX68_000004996-5044

JNJMX68_000006792

JNJMX68_000008982-9004

JNJMX68_000011720-25

JNJMX68_000012858

JNJMX68_000012745-49

JNJMX68_000013019-20

JNJMX68_000013464-66

JNJMX68_000017401-43

JNJMX68_000019698-99

JNJNI000294462

JNJNL61_000000134-36

JNJNL61_000002666-73

JNJNL61_000006431-32

JNJNL61_000008084-89

JNJNL61_000014431-37

JNJNL61_000020359

JNJNL61_000029410-36

JNJNL61_000052427

JNJNL61_000061857

JNJNL61_000063473

JNJNL61_000064366-67

JNJNL61_000079334-35

JNJTALC000716827-45

LUZ000250

LUZ000566-67

LUZ001017-22

LUZ001298-1303

LUZ001326-27

LUZ001441-44

LUZ001719-20

LUZ001873-76

LUZ002733-51

LUZ003202-03

LUZ003204

LUZ003264-67

LUZ004656-65

LUZ005090-91

LUZ005109-10

LUZ005118

LUZ006056

LUZ006507-09

LUZ010145-48

LUZ011817

LUZ011963

LUZ011964-65

LUZ012006-18

LUZ012031-32

LUZ012732-33

LUZ012863-64

LUZ012865-66

LUZ013053-55

LUZ013093

LUZ013094-95

LUZ013367-87

LUZ015111-12

LUZ015663

LUZ020182-86

LUZ021921-29

LUZ022044-50

LUZ022207-08

LUZ023843-35

MBS-CRE Production of Documents 000240-41

PCPC0017629

PCPC0052415

WCD000254-55

After your doctor or health care provider prescribes your ORTHO Diaphragm, 1998.

(JANSSEN000056-65)

Agenda: NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee
Meeting

Annie Yessian Report - Echeverria

Berg v. Johnson & Johnson, Final Jury Instructions

Berg v. Johnson & Johnson, Judgment

Berg v. Johnson & Johnson, Verdict Form October 4, 2013

California State Cosmetics Program from the California Dept of Public Health - Occupational
health Branch - Chemicals known or suspected to cause cancer or reproductive
toxicity (P-31)

California Safe Cosmetics Act 2005

Carl v. J&J; Balderrama v. J&J - Defendants Johnson & Johnson, Johnson & Johnson Consumer Inc., and Imerys Talc America, Inc's joint memorandum of law in support of their motion to exclude plaintiffs' experts' general causation opinions

Cancer Prevention Coalition – November 17, 1994 Citizen’s Petition to FDA seeking carcinogenic labelling on all cosmetic talc products

Cancer Prevention Coalition – May 13, 2008 Citizen’s Petition to FDA seeking a cancer warning on cosmetic talc products

Cesario, S - Powerpoint “Feminine hygiene product use and the risk of ovarian cancer”

Committee on the State of the Science in Ovarian Cancer Research; Board on Health Care Services; Institute of Medicine; National Academies of Sciences, Engineering, and Medicine. Ovarian Cancers: Evolving Paradigms in Research and Care

Cesario, Sandra. PTT-Feminine hygiene product use and the risk of ovarian cancer (*Unpublished*).

Crowley M. (November 12, 2018) Rule 26 report of Michael M. Crowley, PhD regarding the fragrance chemical constituents in Johnson & Johnson Talcum Powder Products

Daniel Cramer Report - Echeverria

Daniel Cramer Supplemental Report - Echeverria

David Steinberg, expert report

David Steinberg, FRAPS Exhibit 14: Statement of Michael M. Landa, J.D.

David Steinberg, CV

David Steinberg publications list

David Steinberg signed verification Di Saia, P. J. (2015). Letter to Kathleen A. Frazier. Unpublished letter.

Defense Expert Reports from Blaes Case: DeSesso; Hoel; Di Saia; Muscat; Hopkins

Deposition Exhibit of John Hopkins – 28 (November 5, 2018)

Deposition Exhibit of Julie Pier – 47 (September 13, 2018)

Deposition Transcript of Alice Blount, *Ingham v. Johnson & Johnson, et al.* (April 13, 2018)

Deposition Transcript & Exhibits - Julie Pier, MDL No. 2738 (September 12 – 13, 2018)

Deposition transcript, 10/19/2012 - John Hopkins

Deposition Transcript & Exhibits - John Hopkins, MDL No. 2738 (Aug. 16 – 17, 2018, Oct.
17, 2018, Nov. 5, 2018)

Deposition Transcript & Exhibits - Joshua Muscat, MDL No. 2738 (Sept. 25, 2018)

Deposition Transcript & Exhibits - Linda Loretz, MDL No. 2738 (July 17, 2018, Oct. 1 – 2,
2018)

Deposition Transcript & Exhibits - Robert Glenn, MDL No. 2738 (Oct. 18, 2018)

D. L. Longo, R. C. Young. Cosmetic talc and ovarian cancer (1979)

D. L. Longo, R. C. Young. Letter to the Editor: Cosmetic talc and ovarian cancer (1979)

Educational Report of Thomas Dydek

Excerpts from S. Sharma Deposition

Expert Report of Laura M. Plunkett, PhD, DABT – Oct. 5, 2016

Expert Report of Jack Siemiatycki, MSc, PhD – Oct. 4, 2016

Fair warning TalcDoc 5 - Exhibit 113 (JNJNL91_000022019)

Fair warning TalcDoc 15

FDA Authority Over Cosmetics April 6, 2015

FDA Response to Citizen's Petition re: Docket Numbers 94P-0420 and FDA-2008-P-0309-
00001/CP

Federal Register – 81 FR 91722 – Banned Devices – Powdered Gloves

Fox v. Johnson & Johnson, Trial Transcript

Godleski, J. J. (2015). Letter to R. Allen Smith, Jr. Unpublished letter.

John J. Godleski, M.D. - Expert Report from Blaes Case

John Godleski Report - Echeverria

John Godleski Supplemental Report - Echeverria

Hopkins, J. (2015). Letter to Gene M. Williams. Unpublished letter.

Johnson's Baby Powder - website, product description

Kemp Hearing Transcript - Douglas Weed

Longo, Rigler, Egeland. MAS Project 14-1852: Below the Waist Application of Johnson & Johnson Baby Powder, September 2017

Longo, Rigler - Analysis of Johnson & Johnson Baby Powder & Valiant Shower to Shower talc products for amphibole (tremolite) asbestos, August 2017

Longo, Rigler - Analysis Report MAS Project #14-1683 Johnson's Baby Powder Sample Set, April 2017

Longo, Rigler - TEM Analysis of historical 1978 Johnson's Baby Powder Sample for amphibole asbestos, February 2018

Longo, Rigler – Expert Report In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (November 14, 2018).

“Making it up as he goes along: Paolo Boffetta, Italian Epidemiologist, distorts power line health risks” - <https://microwavenews.com/news-center/boffetta-post-truth>.

Material Safety Data Sheet from Luzenac America, Inc.; Version 45.0, updated 6/18/08 (Group 1)

Material Safety Data Sheet from Luzenac America, Inc. (Group 3)

Material Safety Data Sheet from Luzenac America, Inc.; Version 2.0, updated 2/26/09 (Group CAN)

Material Safety Data Sheet from Luzenac America, Inc. (Group 1)

MBS Invoices – December 2007, April 2012, May 2013, July 2013, December 20013, January 2015, March 2015

MSDS Sheet, Version 2.0

Muscat, J. E. (2015). Report on the Relationship between Hygienic Use of Talc and the Risk of Ovarian Cancer. Unpublished report.

NPR Article Johnson & Johnson Pledges to Purge Controversial Chemicals April 16, 2015

Ness, R. B. (2015). Report on the question of whether genital talc use causes ovarian cancer. Unpublished report.

Ness, R. Expert Report - Jacqueline Fox

Ness, R. Commentary "A plaintiff's witness in the baby powder case"

NTP "The Report on Carcinogens Tenth Edition - Factsheet"

Omiecinski, C. J. (2015). Opinion on the Relationship Between Chronic Perineal/Genital Exposures to Cosmetic Talc and Ovarian Cancers: Mechanistic Aspects and Biological Plausibility Unpublished report.

Osann, K. (2016). Report on Perineal Talc Exposure and Risk of Ovarian Cancer. Unpublished report.

Personal Care Products Council Letter – July 21, 2009 to FDA re: Comments to FDA Citizen's Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products

Photographs of Johnson's Baby Powder

Photographs of Shower to Shower

Riham Sheble, Shabina Khatri. DOHA News - Johnson's baby powder of Qatar shelves after US cancer lawsuit verdict

Roe. Controversy: Cosmetic talc and ovarian cancer (1979)

Rosenthal, G. J. (2015). Opinion on Relationships Between the Toxicology of Cosmetic Talc and the Pathogenesis of Ovarian Cancer. Unpublished report.

Rosenthal, G - Expert Report from Blaes Case: "Opinion on Relationships Between the Toxicology of Cosmetic Talc and the Pathogenesis of Ovarian Cancer"

Rothman, Pastides, Samet. (2000) Interpretation of epidemiologic studies on talc and ovarian cancer

Slemp v. Johnson & Johnson, et al., Trial Transcript

Summary Minutes of the NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meeting

Talc Removed from 12th RoC- The Rose Sheet October 24, 2005

WHMIS Classification for Talc, non fibrous - CNESST; CAS Number: 14807-96-6

Weed, Douglas. A Report Regarding General Causation and an Evaluation of the Reliability and Validity of the Plaintiffs' Experts' Reports Designated for the Plaintiff, Lori Oules (Feb. 1, 2017)

17. Curriculum Vitae – Jack Siemiatycki

CURRICULUM VITAE

Jack Siemiatycki

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STATISTICAL SUMMARY OF SELECTED ACCOMPLISHMENTS

Publications in peer-reviewed journals	245
Book chapters, IARC Monographs	20
Other publications, reports	42
Book (authored)	1
Invited presentations	173
Conference presentations, posters, abstracts : offered and accepted	181
Grants received as P.I. (number)	36
Grants received as P.I. (\$)	\$15.4M
Grants received as co-investigator (number)	59
Grants received as co-investigator (\$)	\$27.9M
H-factor (google scholar)	64
Instances of participation on expert panels, committees, boards of directors, at invitation of governments or public health agencies or research agencies or universities	126
Grant review panels or referee for external institution or journal editorial boards	65
Honours	several

GENERAL INFORMATION

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EDUCATION

1967 B.Sc. (mathematics); McGill University
1970 M.Sc. (mathematical statistics); McGill University
1976 Ph.D. (epidemiology and medical statistics); McGill University
1977 Post-doctoral (cancer epidemiology); International Agency for Research on Cancer, Lyon

CURRENT ACADEMIC APPOINTMENTS

Professor, Department of Social and Preventive Medicine, Université de Montréal (since 2001)
Cancer Research Society-Guzzo Research Chair in Environment and Cancer, Université de Montréal (since November 2007)
Adjunct Professor, Department of Epidemiology, Biostatistics and Occupational Health, McGill University. (since 1979)
Fellow, Canadian Academy of Health Sciences (since 2008)

PREVIOUS ACADEMIC APPOINTMENTS AND WORK EXPERIENCE

1967-71 Research Fellow; Department of Epidemiology and Health, McGill University.
1970-72 Research Director; Pointe St. Charles Community Clinic, Montréal.
1978 Consultant; International Agency for Research on Cancer, Lyon.
1978-2001 Assistant, then Associate (1979), then full Professor (1983):
Epidemiology Research Center, Institut Armand-Frappier, Laval, Québec.
1982-1986 Associate member, McGill Cancer Center, McGill University.
1996-1997 Visiting Scientist. International Agency for Research on Cancer, Lyon.
2001-2015 Canada Research Chair (Tier 1), Université de Montréal (resigned 2011).
2003-2009 Affiliate Scientist. McLaughlin Centre for Pop'n Health Risk Assessment, Univ of Ottawa.

SIGNIFICANT INTERNAL ADMINISTRATIVE APPOINTMENTS

1982-86 Director, Équipe associée de l'Institut de Recherche en Santé et Sécurité du Travail sur les cancers professionnels (affiliated research team of the Quebec Institute for Occupational Health and Safety on Occupational Cancer).
1988-91 Director, Epidemiology Research Center, Institut Armand-Frappier.
1990-98 Director, Équipe prioritaire de recherche en épidémiologie environnementale du FRSQ. (Priority research team in environmental epidemiology)
1998-2001 Member, Governing Council (Conseil d'administration). Institut national de la recherche scientifique, Université du Québec.
2000-2007 Coordinator. Program of Research in Environmental Epidemiology of Cancer (PREECAN), a national program funded by the National Cancer Institute of Canada.
2002-2005 Associate Director for Population Health Sciences, Research Center of the University of Montréal Hospital Center.

- 2006-2007 Director, Epidemiology program, PhD public health, Université de Montréal.
2006-2014 Director, Axe risques à la santé (Health Risks Division). Centre de recherche du Centre hospitalier de l'Université de Montréal.

SIGNIFICANT INSTITUTIONAL COMMITTEES

- 1979-80 Member of faculty committee to negotiate a collective agreement with the Institut Armand-Frappier administration.
1982-92 Member, Research Council. Institut Armand-Frappier.
1998-2001 Member, Institutional advisory council. Institut Armand-Frappier. Institut national de la recherche scientifique
2002-2006 Comité de direction. Centre de recherche du CHUM
2002-2017 Member, Various committees of the Dept Med Soc et Preventive, including Promotions, and Recruitment.
2006-2009 Member, Various committees established to set up a new School of Public Health at l'Université de Montréal
2006-2014 Comité Scientifique de la Recherche du CHUM.

CURRENT MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES (INVITED)

1. Chair of Scientific Advisory Committee of CONSTANCES, a large prospective cohort established in France, under aegis of INSERM, Ministère de la Santé, and other agencies. Since 2011.
2. Member of Comité national d'épidémiologie en cancérologie. Ministère de la Santé et des Services sociaux, Quebec. Since 2014.
3. Member, Advisory committee to Directors of Cartagene, a Quebec population cohort.

PAST MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES, CONSULTATIONS (INVITED)

1. Expert consultative committee to Commission de la santé et sécurité du travail du Québec on the epidemiologic function of the CSST. 1979-80.
2. President of Organizing Committee of Annual Congress of Quebec Public Health Association, Montréal. 1982.
3. Consultative committee of International Agency for Research on Cancer on feasibility of SEARCH programme. 1982.
4. Canadian representative. International Joint Commission (U.S. and Canada) Committee on the Assessment of Human Health Effects of Great Lakes Water Quality. 1982-89.
5. Task Force on Chemicals in the Environment and Human Reproduction Effects in New Brunswick. 1983-85.
6. Chairman and organizer of international workshop sponsored by International Agency for Research on Cancer, Lyon, on use of job exposure information in cancer case-control studies. 1984.
7. Quebec Government Consultative Committee on Alachlor. 1985-86.
8. Chairman and organizer of the International Joint Commission Workshop on the Role of Epidemiology in Assessing the Effects of Great Lakes Water Quality on Human Health, Scarborough, March 1988. 1986-88.
9. Priority Substances Advisory Panel. Panel established under terms of Canadian Environmental Protection Act by Health and Welfare Canada. 1988.
10. Working Group on Electromagnetic Fields under auspices of Health Effects Institute. 1991.
11. Consultative Committee on Environment-related Cancer Surveillance, LCDC, Health and Welfare Canada. 1993-1996.
12. Consultative Committee on an Investigation of Lung Cancer and Environmental Tobacco Smoke, Environmental Health Directorate, Health Canada. 1994-1995.
13. Working Group on Evaluation of Carcinogenicity of Carbon Black, Printing Trades and Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 1995.

14. Working Group on Human Cancer Risks associated with Chrysotile Asbestos. World Health Organization (IPCS) Geneva, June 1995.
15. Secretariat on Evaluation of Chemopreventive Effect of Aspirin and Other NSAIDS for Cancer. International Agency for Res. on Cancer, Lyon, Apr. 1997.
16. Chair. Symposium on Health Risks of Water Disinfection By-products. Convened by Health Canada. Ottawa. May 1997.
17. Working Group. Meeting on Species-specificity in response to carcinogens. Monograph Programme. International Agency for Res. on Cancer, Lyon, Nov. 1997.
18. Board of Directors. Canadian Society for Epidemiology and Biostatistics. 1997-1999.
19. Working Group. Evaluation of Carcinogenicity of Various Industrial Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, Feb. 1998.
20. Canadian Coalition on Cancer Surveillance. 1997-2002.
21. External site review panel. U.S. National Cancer Institute Epidemiology Branch. June 1999.
22. Organizing Committee for Medical Research Council Workshop on Privacy of Health Data. 1999-2000.
23. Organizing Committee, EPI2001. Joint North American Congress of Canadian Society for Epidemiology and Biostatistics, Society for Epidemiologic Research, American Public Health Association (Epid) and American College of Epidemiology, Toronto, 14 – 16 June 2001. 1999-2001.
24. Coordinator of national initiative of the public health community to provide guidance on the structures and functioning of the new Canadian Institutes of Health Research. 1999-2000.
25. Organizing Committee. World Congress of the International Epidemiological Association, Montréal, 18-22 August 2002. 2001-2002.
26. President. Canadian Society for Epidemiology and Biostatistics. 2001-2003. Member of Board. 1997-1999.
27. Working Group. Evaluation of Carcinogenicity of Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 2003.
28. Jury of Consensus Conference on risks and benefits of vaccination for hepatitis B. For Minister of Health of France. Organized by INSERM and ANAES. Paris 2003.
29. Public Advisory Panel. Vinyl Council of Canada. 1998-2004.
30. Advisory Panel. U.S. National Cancer Institute Brain Tumor Study. 1998-2003.
31. Scientific Advisory Committee. Boeing/UAW Workers' Health Studies. 1999-2005.
32. Institute Advisory Board. Canadian Institutes for Health Research – Institute of Circulatory and Respiratory Health. 2001-2005.
33. National Occupational Research Agenda (NORA). Joint consultative committee for US National Cancer Institute and US National Institute for Occupational Safety and Health. 2002-2005.
34. Canadian Cancer Surveillance Alliance. Consultative committee of Health Canada, Canadian Cancer Society, Provincial Cancer Registries, Statistics Canada. 2002-2003.
35. Co-president. Organizing Committee of Joint SER-CSEB Congress, Toronto 27-30 June 2005. (2004-2005).
36. Chair. Monograph Program Meeting. International Agency for Research on Cancer (WHO), France. February 2006.
37. Advisory Committee on Research Ethics and Databanks. Quebec Health Research Council (FRSQ). 2003-2011.
38. Board of Directors. American College of Epidemiology. 2003-2006.
39. Board of Directors. National Cancer Institute of Canada. 2003-2007.
40. Member Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2005-2009.
41. Elected Chair. Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2008-2009.
42. Scientific Advisory Council Canadian Partnership Against Cancer 2007-2009.
43. Advisory Committee. Occupational Cancer Research Centre of Ontario. Since 2009.
44. Working Group on Cancer Prevention, CPAC, 2007-2010.

45. Subgroup Chair and Working Group Member. Evaluation of Carcinogenicity of Non-Ionizing Radiation, Radiofrequency Electromagnetic Fields. Monograph Programme. International Agency for Research on Cancer, Lyon May 2011.
46. Member of Scientific Advisory Board of Bordeaux cancer research center SIRIC-BRIO, Bordeaux France. Since 2013.
47. Member of external review panel. Helmholtz Center Munich Research Institute. Germany. July 2011.
48. Conseil Scientifique de l'Institut de Recherche en Santé Publique (IReSP). Under aegis of INSERM and Ministère de la Santé, France. 2004-2009.
49. Adviser and expert witness for legal team conducting a major class action lawsuit against the Canadian tobacco industry. 2007-2014.

OTHER SIGNIFICANT EXTERNAL CONSULTATIONS (INVITED)

1. Consultation with Quebec Ministry of Justice regarding compensation for homeowners who were advised to use formaldehyde-base home insulation - 1983.
2. Invited participant. Workshop convened by the Science Council of Canada on the future of Epidemiology in Canada, Ottawa - 1985.
3. Consultation with Government of Alberta regarding the evaluation of a report alleging significant health impact in the environment of a sour-gas plant - 1985.
4. Consultation with Quebec Ministry of Environment regarding health effects of residency near an abandoned toxic waste site in LaSalle, Quebec - 1987.
5. Invited participant. Workshop convened by Canadian Public Health Association, Environment Canada and Health and Welfare Canada on Environmental Impact Assessment, Ottawa - 1987.
6. Invited participant. Annual workshops convened by Health Protection Branch of Health and Welfare Canada to discuss the role of Canada in the SEARCH programme of the International Agency for Research on Cancer, Ottawa - 1987-1989.
7. Consultation with Quebec Cree Band Council regarding a research proposal to study developmental effects of consuming fish with high mercury levels - 1989.
8. Invited participant. Workshop convened by Ontario Industrial Disease Standards Panel on the use of epidemiologic data in workers' compensation, Toronto - December 1989.
9. Invited participant. Workshop convened by National Academy of Sciences (U.S.) on Carcinogenicity of Complex Mixtures, Tucson, Arizona - Jan 1990.
10. Invited participant. Workshop convened by Laboratory Centers for Disease Control, Health and Welfare Canada on Multiple Chemical Sensitivities, Ottawa - May 1990
11. Member of expert advisory panel to the pan-Canadian case-control study of electromagnetic fields and childhood leukemia. Sponsored by Canadian Electrical Assoc, EPRI (U.S.A.), Health and Welfare Canada. 1990-1996.
12. Organizer of Workshop to Plan a Pan-North American Case-control Study of Lung Cancer. Sponsored by Health and Welfare Canada. Toronto. March 1991.
13. Invited participant. Workshop convened by Environmental Health Directorate of Health and Welfare Canada, on Environmental Epidemiology in Canada. Ottawa. March 1992
14. Invited participant. Workshop convened by Harvard Center for Risk Analysis on implementing a new type of risk assessment. Maryland. April 1992.
15. Member of Technical Advisory Panel for epidemiology studies of foundry workers - CIIT. Research Triangle Park, N.C. Feb. 1993
16. Consultant to Health Effects Institute - Asbestos Research, on Options for Characterizing Worker Activities in Buildings, Boston. Feb. 1993.
17. Advisory panel to Laboratory Centers for Disease Control, Health and Welfare Canada, on Environmental Epidemiology under the Green Plan. March 1993.
18. Member of External Advisory Committee. Champlain Adirondack Biosphere Environmental Health Sciences Center, University of Vermont. 1993.
19. Consultant to Michigan Cancer Foundation on a variety of epidemiologic studies. 1993-1996.

20. Invited to address President Clinton's Panel on Cancer regarding priorities in cancer research. Bethesda, MD. April 1994.
21. Invited participant. Science and Technology Review Consultation. Government of Canada. Montréal. September 1994.
22. Invited participant. Strategic planning workshop to reduce Environmental Tobacco Smoking exposure. Laboratory Centre for Disease Control. Health Canada. Oct 1995.
23. Invited participant. Meeting to establish new priorities for funding. National Health Research and Development Programme of Canada. Montréal. Feb 1996.
24. Chair Scientific Advisory Committee for the Dalhousie University study of health effects of environmental and occupational pollution in the area of the Sydney, Nova Scotia steel industry. 1996.
25. Member of two Ministerial missions of the Quebec and Canadian governments to France to discuss with French experts the risks associated with low level exposure to chrysotile asbestos. Paris. Oct 1996.
26. Chair. Meeting of collaborators of European network of studies on lung cancer and smoking.
27. International Agency for Res. on Cancer, Lyon. June 1997.
28. Member of Canadian scientific delegation to United Kingdom to discuss with British experts the risk associated with low level exposure to chrysotile asbestos. London, Sept. 1997.
29. Symposium chair. Workshop to discuss methods of predicting numbers of cases of mesothelioma to be expected in various countries. Paris. Dec. 1997.
30. Invited participant and subgroup reporter. Peer Review on Hazard Assessment and Dose-Response Characterization for the Carcinogenicity of Formaldehyde by the Route of Inhalation. Health Canada and U.S. EPA. Ottawa. March 1998.
31. Co-chair. Workshop to explore the feasibility of an international collaborative study on use of cellular phones and risk of cancer. International Agency for Research on Cancer. Lyon. Feb 1999.
32. Panellist. Consensus Meeting for a Proposed Integrated National Health Surveillance Network. Health Canada. 1999.
33. Invited participant. Medical Research Council Summit Meeting on the new Canadian Institutes of Health Research. Toronto. June, 1999.
34. Invited participant. Planning group for an Institute of Population Health Research in CIHR. Jul-Dec 1999.
35. Invited speaker. Workshop for a Canadian Institute for Genetics Research. May 2000.
36. Invited participant. Workshop to explore the use of prospective cohorts to investigate gene-environment interactions in cancer etiology. National Cancer Institute. Rockville, MD. May 2000.
37. Invited participant. Founding meeting of Canadian Association for Workplace Safety and Health. Montréal. Jan 2001.
38. Invited participant. Workshop to advise Canadian Foundation for Innovation on its role in supporting population health research in Canada. Toronto, Feb 2001.
39. Invited participant. Consultative committee to advise Cancer Care Ontario on priorities in environmental cancer. April 2001.
40. Invited participant. Workshop on national priorities in cancer research. Institute for Cancer Research. CIHR. Toronto. May 2001.
41. Invited participant. Delphi process to advise Canadian Institutes of Health Research on priorities in cancer research. October-December 2001.
42. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
43. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.
44. Member of Advisory Panel. U.S. National Cancer Inst. Study of a Cohort of Chinese Workers Exposed to Benzene. 2002- .
45. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
46. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.

47. Organizer and Session Chair. International Epidemiological Association Meeting. Occupation and Health. Montréal. August, 2002.
48. Co-Organizer and Session Chair. Epidemiological Association Meeting. Asbestos and mesothelioma. Montréal. August, 2002.
49. Session Chair. Epidemiological Association Meeting. Environment and Health. Montréal Aug, 2002.
50. Invited participant. CIHR National Forum to devise a National Research Programme for Environmental Health. Ottawa. Sept 2002.
51. Invited participant. CIHR national forum on privacy of health data. Ottawa, November, 2002.
52. Member. Environmental and Occupational Carcinogens Advisory Group. Canadian Cancer Society. 2002 - 2004.
53. Participant. Meeting to discuss the establishment of a prospective childhood cohort in Canada. CIHR-IPPH. March 2004.
54. Member of working group on national cohort project. National Cancer Research Initiative. January-June 2004.
55. Member of advisory group on development of IDEES, Université de Montréal. January-June 2004.
56. Member, ad-hoc group to explore the feasibility of a Canadian cohort on cancer and chronic disease. 2004-2008.
57. Invited participant. Workshop to discuss the enhancement of population health research in Canada. CIHR-IPPH. June 2004.
58. Invited participant. Workshop on occupational cancer surveillance. Occupational Cancer Research & Surveillance Project (Cancer Care Ontario and the Ontario Workplace Safety & Insurance Board). February 2005.
59. Invited participant. Workshop on long-term large-scale cohorts. CIHR, December 2005.
60. Member. Advisory Scientific Committee. IBM – University of Alabama project on health of IBM manufacturing plant workers. 2006 - 2008.
61. Advisor and meeting participant. Ontario Workplace Safety and Insurance Board. Recommendations on how to develop occupational cancer research in Ontario. Toronto, 2005.
62. Invited participant. Workshop to estimate the burden of occupational cancer in the United Kingdom. UK Health and Safety Executive. Manchester. June 2006.
63. Advisory Committee to British Energy Networks Association. Workshop on the Future Needs of Electromagnetic Fields Occupational Studies in the Electric Utility Industry. Edinburgh. September 2006.
64. Advisory Committee. IARC Monograph Programme Planning of Special Volume 100. Lyon. September 2006.
65. Grant Review Panel. IVRSP. Paris. September 2006.
66. Advisory Committee to CCRA and ICR (CIHR) on the nature of a national cohort platform. Toronto, September 2006.
67. Invited participant. Comité d'éthique de la recherche de la faculté de médecine (CERFM) : Discussion d'un projet soumis pour la création d'une banque de données et de matériaux biologiques (Research Ethics Committee of the Faculty of Medicine: Review of a submitted project to create a bank of data and biologic samples). Université de Montréal. March 2007.
68. Invited participant. Workshop to Design and Implement the Ontario Cohort Consortium Research Platform. Toronto. June 2007.
69. Invited participant. Canadian Cancer Research Agencies. Strategic Planning Consultation in Montréal. May 2009.
70. Invited participant. IARC-NORA workshop to identify gaps of knowledge on occupational carcinogens, Lyon. June 2009.
71. Consultant. State of the science workshop: evaluation of epidemiological data consistency for application in regulatory risk assessment. US EPA and Johns Hopkins School of Public Health. Baltimore. September 2010.
72. Consultant. World Health Organisation. Re-evaluation of Risk Assessments related to DDT exposure. Geneva. November 2010.

73. Invited participant. WHO workshop to develop international guidelines for control of environmental carcinogens. Asturias. March 2011.
74. Session Chair. Discovering occupational carcinogens. Congress of Epidemiology. Montréal June 2011.
75. Invited co-organiser. Symposium of Environment and Cancer. Canadian Cancer Research Conference. Toronto. November 2011.
76. Invited organiser and Chair. Symposium on Cellphones and Cancer. American Association for Cancer Research. Chicago, April 2012.
77. Member Scientific Program Committee for the 2013 Canadian Cancer Research Conference, Toronto. November 2013.
78. Member of Advisory Committee to National Cancer Institute (U.S.) study on carcinogenicity of diesel emissions. 2017.

HONOURS

1. Biographee in various Who's Who in America versions. Since 1982
2. Perron-Desrosiers Prize. Granted by the Governing Council of the Institut Armand-Frappier. 1985.
3. Invited to give the annual Elizabeth Stern Memorial Lecture in U.C.L.A. School of Public Health. 1985.
4. National Health Scholar. National Health Research and Development Programme of Canada. 1988-1998.
5. Visiting Scientist Award. International Agency for Research on Cancer, Lyon. 1996-97.
6. Prix d'excellence. Institut national de la recherche scientifique. Université du Québec. 1999.
7. Distinguished Scientist Award. Medical Research Council, Canada. 1999-2004.
8. Canada Research Chair in Environmental Epidemiology and Population Health. 2001-2015.
9. Distinguished Scientist Lecturer. US National Cancer Institute. Division of Cancer Epidemiology and Genetics. 2006.
10. Cancer Research Society-Guzzo Chair in Environment and Cancer. Since 2007.
11. Fellow Canadian Academy of Health Sciences. Since 2008.
12. Geoffrey R Howe Distinguished Contributions Award, Canadian Society for Epidemiology & Biostatistics. 2011.
13. Ranked top Canadian public health researcher in terms of research productivity by Jarvey et al. 2012.

GRANT REVIEW, JOURNAL REVIEW AND PERSONNEL REVIEW

Associate Editor

American Journal of Epidemiology (1989-1998)

International Journal of Environmental Health (1991-)

Contributing Editor

Journal of Public Health Policy (1982-87)

American Journal of Industrial Medicine (1996-)

The Open Epidemiology Journal (2007-)

Chairman of grant review panels

National Health Research and Development Programme. Canada. (1990-94)

National Cancer Institute of Canada (1994-1995)

Member of grant review panels

40 times

External referee for tenure or promotion of personnel in other institutions

15 times

THESES

1. Siemiatycki J. "Space-time clustering: finding the distribution of a correlation-type statistic". M.Sc. thesis, McGill University, 1971.
2. Siemiatycki J. "Evaluation of strategies for household health surveys". Ph.D. thesis, McGill University, 1976.

ARTICLES PUBLISHED PEER REVIEW

1. Thurlbeck WM, Horowitz I, Siemiatycki J, Dunnill MS, Maisel JC, Pratt P, et al. Intra- and inter-observer variations in the assessment of emphysema. *Archives of Environmental Health*. 1969;18:646-59.
2. Becklake MR, Fournier-Massey G, McDonald JC, Siemiatycki J, Rossiter CE. Lung function in relation to chest radiographic changes in Quebec asbestos workers. *Bulletin de Physio-Pathologie Respiratoire*. 1970;6:637-59.
3. McDonald JC, McDonald AD, Gibbs GW, Siemiatycki J, Rossiter CE. Mortality in the chrysotile asbestos mines and mills of Quebec. *Archives of Environmental Health*. 1971;22:677-86.
4. Siemiatycki J, McDonald AD. Neural tube defects in Quebec: a search for evidence of 'clustering' in time and place. *British Journal of Preventive and Social Medicine*. 1972;26:10-4.
5. Siemiatycki J. Mantel's space-time clustering statistic: computing higher moments and a comparison of various data transforms. *Journal of Statistical Computation & Simulation*. 1978;7:13-31.
6. Siemiatycki J. A comparison of mail, telephone, and home interview strategies for household health surveys. *American Journal of Public Health*. 1979;69(3):238-45.
7. Siemiatycki J, Brubaker G, Geser A. Space-time clustering of Burkitt's lymphoma in east Africa: analysis of recent data and a new look at old data. *International Journal of Cancer*. 1980;25:197-203.
8. Siemiatycki J, Richardson L. Statut socio-économique et utilisation des services de santé à Montréal. *L'Actualité Économique*. 1980(Avril-Juin):194-210.
9. Siemiatycki J, Richardson L, Pless IB. Equality in medical care under national health insurance in Montréal. *New England Journal of Medicine*. 1980;303:10-5.
10. Colle E, Siemiatycki J, West R, Belmonte MM, Crepeau MP, Poirier R, et al. Incidence of juvenile onset diabetes in Montréal - demonstration of ethnic differences and socio-economic class differences. *Journal of Chronic Diseases*. 1981;34(12):611-6.
11. Siemiatycki J, Day NE, Fabry J, Cooper JA. Discovering carcinogens in the occupational environment: a novel epidemiologic approach. *Journal of the National Cancer Institute*. 1981;66(2):217-25.
12. Siemiatycki J, Thomas DC. Biological models and statistical interactions: an example from multistage carcinogenesis. *International Journal of Epidemiology*. 1981;10(4):383-7.
13. Siemiatycki JA, Richardson LJ. Le défi prioritaire en santé communautaire : Élargir notre vision pour atteindre nos véritables objectifs. *L'Union Médicale du Canada*. 1981;110:1008-12.
14. Pampalon R, Siemiatycki J, Blanchet M. Pollution environnementale par l'amiante et santé publique au Québec [Environmental asbestos pollution and public health in Quebec]. *L'Union Médicale du Canada*. 1982;111(5):475-82, 87-89.
15. Siemiatycki J, Gérin M, Richardson L, Hubert J, Kemper H. Preliminary report of an exposure-based, case-control monitoring system for discovering occupational carcinogens. *Teratogenesis, Carcinogenesis, and Mutagenesis*. 1982;2:169-77.
16. *Baumgarten M, Siemiatycki J, Gibbs GW. Validity of work histories obtained by interview for epidemiologic purposes. *American Journal of Epidemiology*. 1983;118(4):583-91.
17. Hours M, Fabry J, Siemiatycki J, Francois R. Diabète insulino-dépendant juvénile. Étude descriptive dans le département du Rhône. *Revue d'épidémiologie et de santé publique*. 1984;32:107-12.
18. Siemiatycki J, Campbell S. Nonresponse bias and early versus all responders in mail and telephone surveys. *American Journal of Epidemiology*. 1984;120(2):291-301.

19. Siemiatycki J, Campbell S, Richardson L, Aubert D. Quality of response in different population groups in mail and telephone surveys. *American Journal of Epidemiology*. 1984;120(2):302-14.
20. *Dewar RAD, Siemiatycki J. A program for point and interval calculation of odds ratios and attributable risks from unmatched case-control data. *International Journal of Bio-Medical Computing*. 1985;16:183-90.
21. Gérin M, Siemiatycki J, Kemper H, Bégin D. Obtaining occupational exposure histories in epidemiologic case-control studies. *Journal of Occupational Medicine*. 1985;27(6):420-6.
22. Siemiatycki J. Long-term funding for epidemiologic research. *Journal of Chronic Diseases*. 1985;38(3):211-2.
23. Thomas DC, Siemiatycki J, Dewar R, Robins J, Goldberg M, Armstrong BG. The problem of multiple inference in studies designed to generate hypotheses. *American Journal of Epidemiology*. 1985;122(6):1080-95.
24. Gérin M, Siemiatycki J, Bégin D, Kemper H, Lakhani R, Nadon L, et al. Dépistage épidémiologique des facteurs cancérigènes de l'environnement de travail montréalais: un premier bilan. *Travail et Santé*. 1986;2(3):S42-S6.
25. *Goldberg MS, Siemiatycki J, Gérin M. Inter-rater agreement in assessing occupational exposure in a case-control study. *British Journal of Industrial Medicine*. 1986;43:667-76.
26. Siemiatycki J, Colle E, Aubert D, Campbell S, Belmonte MM. The distribution of type I (insulin-dependent) diabetes mellitus by age, sex, secular trend, seasonality, time clusters, and space-time clusters: evidence from Montréal, 1971-1983. *American Journal of Epidemiology*. 1986;124(4):545-60.
27. Siemiatycki J, Richardson L, Gérin M, Goldberg M, Dewar R, Déry M, et al. Associations between several sites of cancer and nine organic dusts: results from an hypothesis-generating case-control study in Montréal, 1979-1983. *American Journal of Epidemiology*. 1986;123(2):235-49.
28. Thomas DC, Goldberg M, Dewar R, Siemiatycki J. Statistical methods for relating several exposure factors to several diseases in case-heterogeneity studies. *Statistics in Medicine*. 1986;5:49-60.
29. *Guay D, Siemiatycki J. Historic cohort study in Montréal's fur industry. *American Journal of Industrial Medicine*. 1987;12:181-93.
30. Siemiatycki J, Dewar R, Nadon L, Gérin M, Richardson L, Wacholder S. Associations between several sites of cancer and twelve petroleum-derived liquids. Results from a case-referent study in Montréal. *Scandinavian Journal of Work, Environment and Health*. 1987;13:493-504.
31. Siemiatycki J, Wacholder S, Richardson L, Dewar R, Gérin M. Discovering carcinogens in the occupational environment: methods of data collection and analysis of a large case-referent monitoring system. *Scandinavian Journal of Work, Environment and Health*. 1987;13:486-92.
32. Diabetes Epidemiology Research International Group. Geographic patterns of childhood insulin-dependent diabetes mellitus. *Diabetes*. 1988;37:1113-9.
33. Siemiatycki J. Epidemiologic approaches to evaluation of carcinogens. In: *Living in a Chemical World*. Annals of the New York Academy of Sciences. 1988;534:395-9.
34. Siemiatycki J, Colle E, Campbell S, Dewar R, Aubert D, Belmonte MM. Incidence of IDDM in Montréal by ethnic group and by social class and comparisons with ethnic groups living elsewhere. *Diabetes*. 1988;37(8):1096-102.
35. Siemiatycki J, Gérin M, Stewart P, Nadon L, Dewar R, Richardson L. Associations between several sites of cancer and ten types of exhaust and combustion products. Results from a case-referent study in Montréal. *Scandinavian Journal of Work, Environment and Health*. 1988;14:79-90.
36. Siemiatycki J, Wacholder S, Dewar R, Cardis E, Greenwood C, Richardson L. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. *Journal of Occupational Medicine*. 1988;30(8):617-25.
37. Siemiatycki J, Wacholder S, Dewar R, Wald L, Bégin D, Richardson L, et al. Smoking and degree of occupational exposure: are internal analyses in cohort studies likely to be confounded by smoking status? *American Journal of Industrial Medicine*. 1988;13:59-69.

38. Gérin M, Siemiatycki J, Nadon L, Dewar R, Krewski D. Cancer risks due to occupational exposure to formaldehyde: results of a multi-site case-control study in Montréal. *International Journal of Cancer*. 1989;44:53-8.
39. Siemiatycki J. Friendly control bias. *Journal of Clinical Epidemiology*. 1989;42(7):687-8.
40. Siemiatycki J, Colle E, Campbell S, Dewar RAD, Belmonte MM. Case-control study of IDDM. *Diabetes Care*. 1989;12(3):209-16.
41. Siemiatycki J, Dewar R, Lakhani R, Nadon L, Richardson L, Gerin M. Cancer risks associated with 10 inorganic dusts: results from a case-control study in Montréal. *American Journal of Industrial Medicine*. 1989;16(5):547-67.
42. Siemiatycki J, Dewar R, Richardson L. Costs and statistical power associated with five methods of collecting occupation exposure information for population-based case-control studies. *American Journal of Epidemiology*. 1989;130(6):1236-46.
43. Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. *Diabetes*. 1990;39:858-64.
44. Hours M, Siemiatycki J, Fabry J, Francois R. [Time clustering and temporospatial regrouping study of cases of juvenile diabetes in the district of Rhône (1960-1980)]. *Revue d'épidémiologie et de santé publique*. 1990;38(4):287-95.
45. Terracini B, Siemiatycki J, Richardson L. Cancer incidence and risk factors among Montréal residents of Italian origin. *International Journal of Epidemiology*. 1990;19(3):491-7.
46. *Dewar R, Siemiatycki J, Gérin M. Loss of statistical power associated with the use of a job-exposure matrix in occupational case-control studies. *Applied Occupational & Environmental Hygiene*. 1991;6:508-15.
47. Gérin M, Siemiatycki J. The occupational questionnaire in retrospective epidemiologic studies: recent approaches in community-based studies. *Applied Occupational & Environmental Hygiene*. 1991;6(6):495-501.
48. Payment P, Franco E, Richardson L, Siemiatycki J. Gastrointestinal health effects associated with the consumption of drinking water produced by point-of-use domestic reverse-osmosis filtration units. *Applied and Environmental Microbiology*. 1991;57(4):945-8.
49. Payment P, Richardson L, Siemiatycki J, Dewar R, Edwardes M, Franco E. A randomized trial to evaluate the risk of gastrointestinal disease due to consumption of drinking water meeting current microbiological standards. *American Journal of Public Health*. 1991;81(6):703-8.
50. Bégin D, Gérin M, de Guire L, Siemiatycki J, Adib G. Étude sur la validité des matrices emploi-exposition multisectorielles en hygiène industrielle. *Revue de médecine du travail*. 1992;XIX:74-9.
51. Soskolne CL, Jhangri GS, Siemiatycki J, Lakhani R, Dewar R, Burch JD, et al. Occupational exposure to sulfuric acid in southern Ontario, Canada, in association with laryngeal cancer. *Scandinavian Journal of Work, Environment and Health*. 1992;18(4):225-32.
52. Ursin G, Aragaki CC, Paganini-Hill A, Siemiatycki J, Thompson WD, Haile RW. Oral contraceptives and premenopausal bilateral breast cancer: a case-control study. *Epidemiology*. 1992;3(5):414-9.
53. Payment P, Franco E, Siemiatycki J. Absence of relationship between health effects due to tap water consumption and drinking water quality parameters. *Water Science & Technology*. 1993;27(3/4):137-43.
54. Siemiatycki J. Problems and priorities in epidemiologic research on human health effects related to wiring code and electric and magnetic fields. *Environmental Health Perspectives*. 1993;101(Suppl. 4):135-41.
55. Case BW, Dufresne A, Fraser R, Siemiatycki J, Perrault G, Takahashi K. Decoding occupational history from total lung particulate analysis: Concordance between physico-chemical analysis and occupational histories. *Annals of Occupational Hygiene*. 1994;38(Supplement 1):469-82.
56. Korner-Bitensky N, Wood-Dauphinee S, Siemiatycki J, Shapiro S, Becker R. Health-related information postdischarge: telephone versus face-to-face interviewing. *Archives of Physical Medicine and Rehabilitation*. 1994;75(12):1287-96.

57. Siemiatycki J, Dewar R, Krewski D, Desy M, Richardson L, Franco E. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? *Epidemiology*. 1994;5(1):57-65.
58. Siemiatycki J, Dewar R, Nadon L, Gérin M. Occupational risk factors for bladder cancer: results from a case-control study in Montréal, Quebec, Canada. *American Journal of Epidemiology*. 1994;140(12):1061-80.
59. Takahashi K, Case BW, Dufresne A, Fraser R, Higashi T, Siemiatycki J. Relation between lung asbestos fibre burden and exposure indices based on job history. *Occupational & Environmental Medicine*. 1994;51(7):461-9.
60. Case BW, Dufresne A, Richardson L, Siemiatycki J, Takahashi K. Lung-retained dose following occupational exposure to silica. *Applied Occupational & Environmental Hygiene*. 1995;10(12):1031-6.
61. Nadon L, Siemiatycki J, Dewar R, Krewski D, Gerin M. Cancer risk due to occupational exposure to polycyclic aromatic hydrocarbons. *American Journal of Industrial Medicine*. 1995;28(3):303-24.
62. Siemiatycki J. Future etiologic research in occupational cancer. *Environmental Health Perspectives*. 1995;103 (Suppl 8):209-15.
63. Siemiatycki J, Krewski D, Franco E, Kaiserman M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *International Journal of Epidemiology*. 1995;24(3):504-14.
64. Upfal M, Divine G, Siemiatycki J. Design issues in studies of radon and lung cancer: implications of the joint effect of smoking and radon. *Environmental Health Perspectives*. 1995;103(1):58-63.
65. Ursin G, Paganini-Hill A, Siemiatycki J, Thompson WD, Haile RW. Early adult body weight, body mass index, and premenopausal bilateral breast cancer: data from a case-control study. *Breast Cancer Research and Treatment*. 1995;33(1):75-82.
66. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational risk factors for prostate cancer: results from a case-control study in Montréal, Quebec, Canada. *American Journal of Epidemiology*. 1996;143(4):363-73.
67. *Fritschi L, Siemiatycki J. Melanoma and occupation: results of a case-control study. *Occupational & Environmental Medicine*. 1996;53(3):168-73.
68. *Fritschi L, Siemiatycki J. Lymphoma, myeloma and occupation: results of a case-control study. *International Journal of Cancer*. 1996;67(4):498-503.
69. *Fritschi L, Siemiatycki J, Richardson L. Self-assessed versus expert-assessed occupational exposures. *American Journal of Epidemiology*. 1996;144(5):521-7.
70. Haile RW, Witte JS, Ursin G, Siemiatycki J, Bertolli J, Thompson WD, et al. A case-control study of reproductive variables, alcohol, and smoking in premenopausal bilateral breast cancer. *Breast Cancer Research and Treatment*. 1996;37(1):49-56.
71. *Parent ME, Siemiatycki J, Renaud G. Case-control study of exposure to carbon black in the occupational setting and risk of lung cancer. *American Journal of Industrial Medicine*. 1996;30(3):285-92.
72. Siemiatycki J. Exposure assessment in community-based studies of occupational cancer. *Occupational Hygiene*. 1996;3:41-58.
73. *Parent ME, Siemiatycki J, Menzies R, *Fritschi L, Colle E. Bacille Calmette-Guerin vaccination and incidence of IDDM in Montréal, Canada. *Diabetes Care*. 1997;20(5):767-72.
74. Payment P, Siemiatycki J, Richardson L, Renaud G, Franco E, Prévost M. A prospective epidemiological study of gastrointestinal health effects due to the consumption of drinking water. *International Journal of Environmental Health Research*. 1997;7:5-31.
75. Siemiatycki J, *Fritschi L, Nadon L, Gerin M. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. *American Journal of Industrial Medicine*. 1997;31(3):280-6.
76. Witte JS, Ursin G, Siemiatycki J, Thompson WD, Paganinihill A, Haile RW. Diet and premenopausal bilateral breast cancer - a case-control study. *Breast Cancer Research and Treatment*. 1997;42(3):243-51.

77. Boffetta P, Burdorf A, Goldberg M, Merler E, Siemiatycki J. Towards the coordination of European research on the carcinogenic effects of asbestos. *Scandinavian Journal of Work, Environment and Health*. 1998;24(4):312-7.
78. *Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *New England Journal of Medicine*. 1998;338(22):1565-71.
79. Gerin M, Siemiatycki J, Desy M, Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene - results of a case-control study in Montréal. *American Journal of Industrial Medicine*. 1998;34(2):144-56.
80. Hu SW, Hertz-Picciotto I, Siemiatycki J. When to be skeptical of negative studies: pitfalls in evaluating occupational risks using population-based case-control studies. *Canadian Journal of Public Health Revue Canadienne de Sante Publique*. 1998;90(2):138-42.
81. *Parent ME, Siemiatycki J, Fritschi L. Occupational exposures and gastric cancer. *Epidemiology*. 1998;9(1):48-55.
82. Siemiatycki J, Boffetta P. Invited commentary - is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study? *American Journal of Epidemiology*. 1998;148(2):143-7.
83. Stewart PA, Stewart WF, Siemiatycki J, Heineman EF, Dosemeci M. Questionnaires for collecting detailed occupational information for community-based case control studies. *American Industrial Hygiene Association Journal*. 1998;59(1):39-44.
84. Goldberg MS, Siemiatycki J, Dewar R, Desy M, Riberdy H. Risks of developing cancer relative to living near a municipal solid waste landfill site in Montréal, Quebec, Canada. *Archives of Environmental Health*. 1999;54(4):291-6.
85. *Dumas S, Parent ME, Siemiatycki J, Brisson J. Rectal cancer and occupational risk factors: A hypothesis-generating, exposure-based case-control study. *International Journal of Cancer*. 2000;87(6):874-9.
86. Parent ME, Hua Y, Siemiatycki J. Occupational risk factors for renal cell carcinoma in Montréal. *American Journal of Industrial Medicine*. 2000;38(6):609-18.
87. Parent ME, Siemiatycki J, Fritschi L. Workplace exposures and oesophageal cancer. *Occupational & Environmental Medicine*. 2000;57(5):325-34.
88. Pohlabein H, Boffetta P, Ahrens W, Merletti F, Agudo A, Benhamou E,Siemiatycki J, et al. Occupational risks for lung cancer among nonsmokers. *Epidemiology*. 2000;11(5):532-8.
89. Weston TL, Aronson KJ, Siemiatycki J, Howe GR, Nadon L. Cancer mortality among males in relation to exposures assessed through a job-exposure matrix. *International Journal of Occupational and Environmental Health*. 2000;6(3):194-202.
90. Boffetta P, Gaborieau V, Nadon L, Parent MF, Weiderpass E, Siemiatycki J. Exposure to titanium dioxide and risk of lung cancer in a population-based study from Montréal. *Scandinavian Journal of Work, Environment and Health*. 2001;27(4):227-32.
91. Goldberg MS, Parent ME, Siemiatycki J, Desy M, Nadon L, Richardson L, et al. A case-control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. *American Journal of Industrial Medicine*. 2001;39(6):531-46.
92. Parent ME, Siemiatycki J. Occupation and prostate cancer. *Epidemiologic Reviews*. 2001;23(1):138-43.
93. *Sharpe CR, Siemiatycki J. Joint effects of smoking and body mass index on prostate cancer risk. *Epidemiology*. 2001;12(5):546-51.
94. *Sharpe CR, Siemiatycki J. Case-control study of alcohol consumption and prostate cancer risk in Montréal, Canada. *Cancer Causes and Control*. 2001;12(7):589-98.
95. *Sharpe CR, Siemiatycki J, Parent MB. Activities and exposures during leisure and prostate cancer risk. *Cancer Epidemiology, Biomarkers and Prevention*. 2001;10(8):855-60.
96. Siemiatycki J. Should Canadian health care professionals support the call for a worldwide ban on asbestos? *Canadian Medical Association Journal*. 2001;164(4):495-7.

97. Camus M, Siemiatycki J, Case BW, Désy M, Richardson L, Campbell S. Risk of mesothelioma among women living near chrysotile mines versus US EPA asbestos risk model: preliminary findings. *Annals of Occupational Hygiene*. 2002;46(Suppl 1):95-8.
98. Case BW, Camus M, Richardson L, Parent M, Désy M, Siemiatycki J. Preliminary findings for pleural mesothelioma among women in the Québec chrysotile mining regions. *Annals of Occupational Hygiene*. 2002;46(Suppl 1):128-31.
99. Leffondré K, Abrahamowicz M, Siemiatycki J, *Rachet B. Modeling smoking history: a comparison of different approaches. *American Journal of Epidemiology*. 2002;156(9):813-23.
100. *Sharpe CR, Siemiatycki J. Consumption of non-alcoholic beverages and prostate cancer risk. *European Journal of Cancer Prevention*. 2002;11(5):497-501.
101. *Sharpe CR, Siemiatycki J, *Rachet B. Effects of alcohol consumption on the risk of colorectal cancer among men by anatomical subsite (Canada). *Cancer Causes and Control*. 2002;13(5):483-91.
102. *Sharpe CR, Siemiatycki JA, *Rachet BP. The effects of smoking on the risk of colorectal cancer. *Diseases of the Colon and Rectum*. 2002;45(8):1041-50.
103. Siemiatycki J. Commentary: Epidemiology on the side of the angels. *International Journal of Epidemiology*. 2002;31(5):1027-9.
104. Fritschi L, Nadon L, Benke G, Lakhani R, Latreille B, Parent ME, ... Siemiatycki J. Validation of expert assessment of occupational exposures. *American Journal of Industrial Medicine*. 2003;43(5):519-22.
105. Krewski D, Burnett RT, Goldberg MS, Abrahamowicz M, Siemiatycki J, Jerrett M, et al. Rejoinder: Reanalysis of the Harvard Six Cities Study and American Cancer Society study of particulate air pollution and mortality. *Journal of Toxicology & Environmental Health Part A*. 2003;66(16-19):1715-22.
106. Krewski D, Burnett RT, Goldberg MS, Hoover BK, Siemiatycki J, Jerrett M, et al. Overview of the reanalysis of the Harvard Six Cities Study and American Cancer Society Study of particulate air pollution and mortality. *Journal of Toxicology & Environmental Health Part A*. 2003;66(16-19):1507-51.
107. Leffondré K, Abrahamowicz M, Siemiatycki J. Evaluation of Cox's model and logistic regression for matched case-control data with time-dependent covariates: a simulation study. *Statistics in Medicine*. 2003;22(24):3781-94.
108. Leffondré K, Abrahamowicz M, Siemiatycki J, Rachet B. Re: Modeling smoking history: a comparison of different approaches. *American Journal of Epidemiology*. 2003;158(4):393-4.
109. Rachet B, Abrahamowicz M, Sasco AJ, Siemiatycki J. Estimating the distribution of lag in the effect of short-term exposures and interventions: adaptation of a non-parametric regression spline model. *Statistics in Medicine*. 2003;22(14):2335-63.
110. Siemiatycki J, Krewski D, Shi Y, Goldberg MS, Nadon L, Lakhani R. Controlling for potential confounding by occupational exposures. *Journal of Toxicology & Environmental Health Part A*. 2003;66(16-19):1591-603.
111. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondré K. A flexible modeling approach to estimating the component effects of smoking behavior on lung cancer. *Journal of Clinical Epidemiology*. 2004;57(10):1076-85.
112. Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. Listing occupational carcinogens; see errata: 113 (2); A 89. *Environmental Health Perspectives*. 2004;112(15):1447-59.
113. Toraason M, Albertini R, Bayard S, Bigbee W, Blair A, Boffetta P, ... Siemiatycki J, et al. Applying new biotechnologies to the study of occupational cancer - A workshop summary. *Environmental Health Perspectives*. 2004;112(4):413-6.
114. Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Abrahamowicz M, White WH. Validation of the Harvard Six Cities Study of particulate air pollution and mortality. *N Engl J Med*. 2004;350(2):198-9.
115. Infante-Rivard C, Siemiatycki J, Lakhani R, Nadon L. Maternal exposure to occupational solvents and childhood leukemia. *Environmental Health Perspectives*. 2005;113(6):787-92.

116. Krewski D, Burnett RT, Goldberg M, Hoover K, Siemiatycki J, Abrahamowicz M, et al. Reanalysis of the Harvard Six Cities Study, part II: sensitivity analysis. *Inhalation Toxicology*. 2005;17(7-8):343-53.
117. Krewski D, Burnett RT, Goldberg M, Hoover K, Siemiatycki J, Abrahamowicz M, et al. Reanalysis of the Harvard Six Cities Study, part I: validation and replication. *Inhalation Toxicology*. 2005;17(7-8):335-42.
118. *Rousseau MC, Parent ME, Siemiatycki J. Comparison of self-reported height and weight by cancer type among men from Montréal, Canada. *European Journal of Cancer Prevention*. 2005;14(5):431-8.
119. *Rousseau MC, Straif K, Siemiatycki J. IARC carcinogen update. *Environmental Health Perspectives*. 2005;113(9):A580-A1.
120. Siemiatycki J. Synthesizing the lifetime history of smoking. *Cancer Epidemiology, Biomarkers and Prevention*. 2005;14(10):2294-5.
121. Siemiatycki J. Opportunités et défis en épidémiologie environnementale. *Bulletin d'Information en Santé environnementale*. 2005;16(5):3.
122. Straif K, Cardis E, Boffeta P, Rousseau MC, Siemiatycki J. ELF MFs: Straif et al. respond. *Environmental Health Perspectives*. 2005;113(11):A727.
123. Baan R, Straif K, Grosse Y, Secretan W, El Ghissassi F, Coglianò V, WHO IARC Monograph Working Group. Carcinogenicity of carbon black, titanium dioxide, and talc. *Lancet Oncology*. 2006;7(4):295-6.
124. *Benedetti A, Parent ME, Siemiatycki J. Consumption of alcoholic beverages and risk of lung cancer: results from two case-control studies in Montréal, Canada. *Cancer Causes and Control*. 2006;17(4):469-80.
125. Leffondré K, Abrahamowicz M, Xiao Y, Siemiatycki J. Modelling smoking history using a comprehensive smoking index: application to lung cancer. *Statistics in Medicine*. 2006;25(24):4132-46.
126. *Ramanakumar AV, Parent ME, Menzies D, Siemiatycki J. Risk of lung cancer following nonmalignant respiratory conditions: evidence from two case-control studies in Montréal, Canada. *Lung Cancer*. 2006;53(1):5-12.
127. *Rousseau MC, Parent ME, Pollak MN, Siemiatycki J. Diabetes mellitus and cancer risk in a population-based case-control study among men from Montréal, Canada. *International Journal of Cancer*. 2006;118(8):2105-9.
128. Cardis E, Richardson L, Deltour I, Armstrong B, Feychting M, Johansen C, ... Siemiatycki J, et al. The INTERPHONE study: design, epidemiological methods, and description of the study population. *European Journal of Epidemiology*. 2007;22(9):647-64.
129. Parent ME, Rousseau MC, Boffetta P, Cohen A, Siemiatycki J. Exposure to diesel and gasoline engine emissions and the risk of lung cancer. *American Journal of Epidemiology*. 2007;165(1):53-62.
130. *Ramanakumar AV, Parent ME, Siemiatycki J. Risk of lung cancer from residential heating and cooking fuels in Montréal, Canada. *American Journal of Epidemiology*. 2007;165(6):634-42.
131. Rousseau MC, Parent ME, Nadon L, Latreille B, Siemiatycki J. Occupational exposure to lead compounds and risk of cancer among men: a population-based case-control study. *American Journal of Epidemiology*. 2007;166(9):1005-14.
132. Siemiatycki J. Investigating cancer risks related to asbestos and other occupational carcinogens. *Occupational & Environmental Medicine*. 2007;64(8):500-1.
133. Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal use of talc and risk of ovarian cancer. *Journal of Epidemiology and Community Health*. 2008;62(4):358-60.
134. *Pintos J, Parent ME, Rousseau MC, Case BW, Siemiatycki J. Occupational exposure to asbestos and man-made vitreous fibers, and risk of lung cancer: Evidence from two case-control studies in Montréal, Canada. *Journal of Occupational and Environmental Medicine*. 2008;50(11):1273-81.
135. *Ramanakumar AV, Nadon L, Siemiatycki J. Exposures in painting related occupations and risk of selected cancers: Results from a case-control study in Montréal. *American Journal of Industrial Medicine*. 2008;51(6):419-27.

136. *Ramanakumar AV, Parent ME, Latreille B, Siemiatycki J. Risk of lung cancer following exposure to carbon black, titanium dioxide and talc: results from two case-control studies in Montréal. *International Journal of Cancer*. 2008;122(1):183-9.
137. Rousseau MC, Parent M-É, Nadon L, Latreille B, Siemiatycki J. Re: Occupational exposure to lead compounds and risk of cancer among men: a population-based case-control study. *American Journal of Epidemiology*. 2008;168(10):1217-8.
138. *Benedetti A, Parent ME, Siemiatycki J. Lifetime consumption of alcoholic beverages and risk of 13 types of cancer in men: Results from a case-control study in Montréal. *Cancer Detection and Prevention*. 2009;32(5-6):352-62.
139. Koushik A, Parent ME, Siemiatycki J. Characteristics of menstruation and pregnancy and the risk of lung cancer in women. *International Journal of Cancer*. 2009;125(10):2428-33.
140. Parent ME, Désy M, Siemiatycki J. Does exposure to agricultural chemicals increase the risk of prostate cancer among farmers? *McGill Journal of Medicine*. 2009;12(1):70-7.
141. Pintos J, Parent ME, Case BW, Rousseau MC, Siemiatycki J. Risk of mesothelioma and occupational exposure to asbestos and man-made vitreous fibers: evidence from two case-control studies in Montréal, Canada. *Journal of Occupational and Environmental Medicine*. 2009;51(10):1177-84.
142. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, WHO IARC Monograph Working Group. A review of human carcinogens--part C: metals, arsenic, dusts, and fibres. *Lancet Oncology*. 2009;10(5):453-4.
143. Vrijheid M, Armstrong BK, Bedard D, Brown J, Deltour I, Iavarone I, ... Richardson L, ... Siemiatycki J, et al. Recall bias in the assessment of exposure to mobile phones. *Journal of Exposure Science & Environmental Epidemiology*. 2009;19(4):369-81.
144. Vrijheid M, Richardson L, Armstrong BK, Auvinen A, Berg G, Carroll M, ... Siemiatycki J, et al. Quantifying the impact of selection bias caused by nonparticipation in a case-control study of mobile phone use. *Annals of Epidemiology*. 2009;19(1):33-41.
145. *Beveridge R, Pintos J, Parent ME, Asselin J, Siemiatycki J. Lung cancer risk associated with occupational exposure to nickel, chromium VI, and cadmium in two population-based case-control studies in Montréal. *American Journal of Industrial Medicine*. 2010;53(5):476-85.
146. El-Zein M, Parent ME, Ka K, Siemiatycki J, St-Pierre Y, Rousseau MC. History of asthma or eczema and cancer risk among men: a population-based case-control study in Montréal, Quebec, Canada. *Annals of Allergy, Asthma, and Immunology*. 2010;104(5):378-84.
147. Leffondre K, Wynant W, Cao ZR, Abrahamowicz M, Heinze G, Siemiatycki J. A weighted Cox model for modelling time-dependent exposures in the analysis of case-control studies. *Statistics in Medicine*. 2010;29(7-8 Special Issue SI):839-50.
148. *Momoli F, Abrahamowicz M, Parent ME, Krewski D, Siemiatycki J. Analysis of multiple exposures: an empirical comparison of results from conventional and semi-bayes modeling strategies. *Epidemiology*. 2010;21(1):144-51.
149. The INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *International Journal of Epidemiology*. 2010;39(3):675-94.
150. *Vida S, Pintos J, Parent ME, Lavoué J, Siemiatycki J. Occupational exposure to silica and lung cancer: pooled analysis of two case-control studies in Montréal, Canada. *Cancer Epidemiology, Biomarkers and Prevention*. 2010;19(6):1602-11.
151. Ward EM, Schulte PA, Straif K, Hopf NB, Caldwell JC, Carreon T, ... Siemiatycki J, et al. Research recommendations for selected IARC-classified agents. *Environmental Health Perspectives*. 2010;118(10):1355-62.
152. Baan R, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, IARC Monograph Working Group. Carcinogenicity of radiofrequency electromagnetic fields. *Lancet Oncology*. 2011;12(7):624-6.

153. Nkosi TM, Parent ME, Siemiatycki J, Pintos J, Rousseau MC. Comparison of indicators of material circumstances in the context of an epidemiological study. *BMC Medical Research Methodology*. 2011;11:108.
154. Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Bruske I, ... Siemiatycki J, Pintos J, et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. *American Journal of Respiratory and Critical Care Medicine*. 2011;183(7):941-8.
155. Olsson AC, Vermeulen R, Kromhout H, Peters S, Gustavsson P, Bruske I, Siemiatycki J, Pesch B, Bruning T. Rejoinder to Commentary on Exposure to diesel motor exhaust and lung cancer by Bunn and Hesterberg. *American Journal of Respiratory and Critical Care Medicine*. 2011;184: 2010-2011.
156. Parent ME, Rousseau MC, El-Zein M, Latreille B, Desy M, Siemiatycki J. Occupational and recreational physical activity during adult life and the risk of cancer among men. *Cancer Epidemiology*. 2011;35(2):151-9.
157. *Ramanakumar AV, Parent ME, Richardson L, Siemiatycki J. Exposures in painting-related occupations and risk of lung cancer among men: results from two case-control studies in Montréal. *Occupational & Environmental Medicine*. 2011;68(1):44-51.
158. Soskolne CL, Jhangri GS, Scott HM, Brenner DR, Siemiatycki J, Lakhani R, et al. A population-based case-control study of occupational exposure to acids and the risk of lung cancer: evidence for specificity of association. *International Journal of Occupational and Environmental Health*. 2011;17(1):1-8.
159. *Christensen KY, Naidu A, Parent ME, Pintos J, Abrahamowicz M, Siemiatycki J, et al. The risk of lung cancer related to dietary intake of flavonoids. *Nutrition & Cancer-An International Journal*. 2012;64(7):964-74.
160. Labreche F, Case BW, Ostiguy G, Chalaoui J, Camus M, Siemiatycki J. Pleural mesothelioma surveillance: validity of cases from a tumour registry. *Canadian Respiratory Journal*. 2012;19(2):103-7.
161. Lavoué J, Pintos J, Van Tongeren M, Kincl L, Richardson L, Kauppinen T, ... Siemiatycki J. Comparison of exposure estimates in the Finnish job-exposure matrix FINJEM with a JEM derived from expert assessments performed in Montréal. *Occupational & Environmental Medicine*. 2012;69(7):465-71.
162. Nadalin V, Kreiger N, Parent ME, Salmoni A, Sass-Kortsak A, Siemiatycki J, et al. Prostate cancer and occupational whole-body vibration exposure. *Annals of Occupational Hygiene*. 2012;56(8):968-74.
163. Nkosi TM, Parent ME, Siemiatycki J, Rousseau MC. Socioeconomic position and lung cancer risk: how important is the modeling of smoking? *Epidemiology*. 2012;23(3):377-85.
164. Olsson A, Vermeulen R, Kromhout H, Peters S, Gustavsson P, Bruske I, Siemiatycki J, et al. The impact of selection bias due to increasing response rates among population controls in occupational case-control studies: response. *American Journal of Respiratory and Critical Care Medicine*. 2012;185(1):106-7.
165. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. Night work and the risk of cancer among men. *American Journal of Epidemiology*. 2012;176(9):751-9.
166. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. Parent et al. Respond to "shift work and cancer". *American Journal of Epidemiology*. 2012;176(9):764-5.
167. Pesch B, Kendzia B, Gustavsson P, Jockel KH, Johnen G, Pohlabein H, ... Siemiatycki J, et al. Cigarette smoking and lung cancer-relative risk estimates for the major histological types from a pooled analysis of case-control studies. *International Journal of Cancer*. 2012;131(5):1210-9.
168. Peters S, Kromhout H, Olsson AC, Wichmann HE, Bruske I, Consonni D, ... Siemiatycki J, et al. Occupational exposure to organic dust increases lung cancer risk in the general population. *Thorax*. 2012;67(2):111-6.
169. Pintos J, Parent ME, Richardson L, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer: evidence from two case-control studies in Montréal, Canada. *Occupational & Environmental Medicine*. 2012;69(11):787-92.
170. *Vallièrès E, Pintos J, Lavoué J, Parent ME, Rachet B, Siemiatycki J. Exposure to welding fumes increases lung cancer risk among light smokers but not among heavy smokers: evidence from two case-control studies in Montréal. *Cancer Medicine*. 2012;1(1):47-58.

171. *Al-Zoughool M, Pintos J, Richardson L, Parent ME, Ghadirian P, Krewski D. Exposure to environmental tobacco smoke (ETS) and risk of lung cancer in Montréal: a case-control. *Environmental Health*. 2013;12(112):1-8.
172. Behrens T, Kendzia B, Treppmann T, Olsson A, Jockel KH, Gustavsson P, ... Siemiatycki J, et al. Lung cancer risk among bakers, pastry cooks and confectionary makers: the SYNERGY study. *Occupational & Environmental Medicine*. 2013;70(11):810-4.
173. *Christensen KY, *Vizcaya D, Richardson H, Lavoué J, Aronson K, Siemiatycki J. Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montréal. *Journal of Occupational and Environmental Medicine*. 2013;55(2):198-208.
174. El-Zein M, Parent ME, Nicolau B, Koushik A, Siemiatycki J, Rousseau MC. Body mass index, lifetime smoking intensity and lung cancer risk. *International Journal of Cancer*. 2013;133(7):1721-31.
175. Kendzia B, Behrens T, Jockel KH, Siemiatycki J, Kromhout H, Vermeulen R, et al. Welding and lung cancer in a pooled analysis of case-control studies. *American Journal of Epidemiology*. 2013;178(10):1513-25.
176. *Lacourt A, Cardis E, Pintos J, Richardson L, Kincl L, Benke G, et al. INTEROCC case-control study: lack of association between glioma tumors and occupational exposure to selected combustion products, dusts and other chemical agents - art. no. 340. *BMC Public Health*. 2013;13(340):12.
177. *Mahboubi A, Koushik A, Siemiatycki J, Lavoué J, Rousseau MC. Assessment of the effect of occupational exposure to formaldehyde on the risk of lung cancer in two Canadian population-based case-control studies. *Scandinavian Journal of Work, Environment and Health*. 2013;39(4):401-10.
178. Olsson AC, Xu YW, Schuz J, Vlaanderen J, Kromhout H, Vermeulen R, ... Siemiatycki J, Richardson L, et al. Lung cancer risk among hairdressers: a pooled analysis of case-control studies conducted between 1985 and 2010. *American Journal of Epidemiology*. 2013;178(9):1355-65.
179. Turner MC, Krewski D, Armstrong BK, Chetrit A, Giles GG, Hours M, ... Siemiatycki J, et al. Allergy and brain tumors in the INTERPHONE study: pooled results from Australia, Canada, France, Israel, and New Zealand. *Cancer Causes and Control*. 2013;24(5):949-60.
180. van Tongeren M, Kincl L, Richardson L, Benke G, Figuerola J, Kauppinen T, ... Lavoué J, ... The INTEROCC Study Group. Assessing occupational exposure to chemicals in an international epidemiological study of brain tumours. *Annals of Occupational Hygiene*. 2013;57(5):610-26.
181. *Vizcaya D, *Christensen KY, Lavoué J, Siemiatycki J. Risk of lung cancer associated with six types of chlorinated solvents: results from two case-control studies in Montréal, Canada. *Occupational & Environmental Medicine*. 2013;70(2):81-5.
182. *Wynant W, Siemiatycki J, Parent ME, Rousseau MC. Occupational exposure to lead and lung cancer: results from two case-control studies in Montréal, Canada. *Occupational & Environmental Medicine*. 2013;70(3):164-70.
183. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. Re: "night work and the risk of cancer among men" reply. *American Journal of Epidemiology*. 2013;177(10):1166-7.
184. El-Zein M, Parent ME, Siemiatycki J, Rousseau MC. History of allergic diseases and lung cancer risk. *Annals of Allergy, Asthma, and Immunology*. 2014;112(3):230-6.
185. McLean D, Fleming S, Turner MC, Kincl L, Richardson L, Benke G, ... Siemiatycki J, et al. Occupational solvent exposure and risk of meningioma: results from the INTEROCC multicentre case-control study. *Occupational & Environmental Medicine*. 2014;71(4):253-8.
186. Siemiatycki J, Karp I, Sylvestre MP, Pintos J. Estimating the proportion of cases of lung cancer legally attributable to smoking: a novel approach for class actions against the tobacco industry. *American Journal of Public Health*. 2014;104(8):e60-e6.
187. Turner MC, Benke G, Bowman JD, Figuerola J, Fleming S, Hours M, ... Richardson L, ... Siemiatycki J, et al. Occupational exposure to extremely low-frequency magnetic fields and brain tumor risks in the INTEROCC study. *Cancer Epidemiology, Biomarkers and Prevention*. 2014;23(9):1863-72.

188. *Vida S, Richardson L, Cardis E, Krewski D, McBride M, Parent ME, ... Siemiatycki J. Brain tumours and cigarette smoking: analysis of the INTERPHONE Canada case-control study. *Environmental Health*. 2014;13:55.
189. Vlaanderen J, Portengen L, Schuz J, Olsson A, Pesch B, Kendzia B, ... Siemiatycki J, et al. Effect modification of the association of cumulative exposure and cancer risk by intensity of exposure and time since exposure cessation: a flexible method applied to cigarette smoking and lung cancer in the SYNERGY study. *American Journal of Epidemiology*. 2014;179(3):290-8.
190. Denholm R, Schuz J, Straif K, Stucker I, Jockel KH, Brenner DR, ... Siemiatycki J, et al. Is previous respiratory disease a risk factor for lung cancer? *American Journal of Respiratory and Critical Care Medicine*. 2014;190(5):549-59.
191. Vila J, Bowman JD, Kincl L, Conover DL, van Tongeren M, Figuerola J, Richardson L, Cardis E and INTEROCC Study Group. Development of a source-based approach to assessing occupational exposure to electromagnetic fields in the INTEROCC study [abstract]. *Occupational & Environmental Medicine*. 2014;71 (Suppl 1): A35-A36.
192. Bigert C, Gustavsson P, Straif K, Pesch B, Bruning T, Kendzia B, ... Siemiatycki J, et al. Lung cancer risk among cooks when accounting for tobacco smoking: a pooled analysis of case-control studies from Europe, Canada, New Zealand, and China. *Journal of Occupational and Environmental Medicine*. 2015;57(2):202-9.
193. *Valli  res E, Pintos J, Parent ME, Siemiatycki J. Occupational exposure to wood dust and risk of lung cancer in two population-based case-control studies in Montr  al, Canada. *Environmental Health*. 2015;14(1):1-9.
194. *Christensen K Y, Lavou   J, Rousseau M-C, Siemiatycki J. Lack of a protective effect of cotton dust on risk of lung cancer: evidence from two population-based case-control studies. *BMC Cancer*. 2015;15: 212.
195. Consonni D, De Matteis S, Pesatori AC, Bertazzi PA, Olsson AC, Kromhout H, ... Siemiatycki J, et al. Lung cancer risk among bricklayers in a pooled analysis of case-control studies. *International Journal of Cancer*. 2015;136(2):360-71.
196. Pearce NE, Blair A, Vineis P, Ahrens W, Andersen A, Anto JM, ... Siemiatycki J, et al. IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans. *Environ Health Perspect* 2015;(6):507-14.
197. Pesch B, Kendzia B, Hauptmann K, Van Gelder R, Stamm R, ... Siemiatycki J, Lavou   J, J  ckel KH, Br  ning T. Airborne exposure to inhalable hexavalent chromium in welders and other occupations: Estimates from the German MEGA database. *International journal of hygiene and environmental health*. 2015;218(5):500-06.
198. Taeger D, Pesch B, Kendzia B, Behrens T, ... Siemiatycki J, et al. Lung Cancer among Coal Miners, Ore Miners and Quarrymen - Smoking-adjusted Risk Estimates from the Synergy Pooled Analysis of Case-Control Studies. *Scandinavian Journal of Work, Environment and Health*. 2015;July.
199. *Lacourt A, Lavou   J, Pintos J, Siemiatycki J. Lung cancer risk in the construction industry: results from two case-control studies in Montr  al. *BMC Public Health*. 2015;15:941. doi: 10.1186/s12889-015-2237-9.
200. *Liu A, Abrahamowicz M, Siemiatycki J. Conditions for confounding of interactions. *Pharmacoepidemiology & Drug Safety*. 2015;25(3):287-296.
201. Bigert C, Gustavsson P, Straif K, Taeger D, Pesch B, Kendzia B, ... Siemiatycki J, Lavou   J, et al. Lung cancer risk among firefighters when accounting for tobacco smoking – preliminary results from a pooled analysis of case-control studies from Europe, Canada, New Zealand and China. *Journal of Occupational and Environmental Medicine*. Sep 2016, 73 (Suppl 1) A128; DOI: 10.1136/oemed-2016-103951.350
202. Vila J, Bowman JD, Richardson L, Kincl L, Conover DL, McLean D, Mann S, Vecchia P, van Tongeren M, Cardis E and INTEROCC Study Group. A Source-based Measurement Database for Occupational Exposure Assessment of Electromagnetic Fields in the INTEROCC Study: A Literature Review Approach. *Annals of Occupational Hygiene*. 2016;60(2):184-204. doi:10.1093/annhyg/mev076
203. * Kirkham TL, Siemiatycki J, Labreche F, Lavou   J. Impact of aggregating exposure information from cases and controls when building a population-based job-exposure matrix from past expert evaluations. *Occupational & Environmental Medicine*. 2016;73(7):474-481. doi:10.1136/oemed-2014-102690

204. Karp I, Sylvestre MP, Abrahamowicz M, Leffondre K, Siemiatycki J. Bridging the etiologic and prognostic outlooks in individualized assessment of absolute risk of an illness: application in lung cancer. *European Journal of Epidemiology*. 2016;1-9. doi 10.1007/s10654-016-0180-4.
205. *Carrier M, Apparicio P, Kestens Y, Ségin A-M, Pham H, Crouse D, Siemiatycki J. Application of a global environmental equity index in Montréal: diagnostic and further implications. *Annals of the American Association of Geographers*. 2016;106(6),1268-1285.
206. Behrens T, Gross I, Siemiatycki J, Conway D.I, Olsson A, Stücker I, et al. Occupational prestige, social mobility and the association with lung cancer in men. *BMC Cancer*. 2016;16:395. doi: 10.1186/s12885-016-2432-9
207. Vila J, Bowman JD, Figuerola J, Moríña D, Kincl L, Richardson L, Cardis E, and the INTEROCC Study Group, on behalf of the CREAL. Development of a source-exposure matrix for occupational exposure assessment of electromagnetic fields in the INTEROCC study. *Journal of Exposure Science and Environmental Epidemiology*. 2016;Nov 9. doi:10.1038/jes.2016.60.
208. Turner M, Sadetzki S, Langer CE, Villegas R, ... Parent ME, Richardson L, Siemiatycki J, et al. Investigation of bias related to differences between case and control interview dates in five INTERPHONE countries. *Annals of Epidemiology*. 2016;26:827-832.
209. *Pasquet R, Karp I, Siemiatycki J, Koushik A. The consumption of coffee and black tea and the risk of lung cancer. *Annals of Epidemiology*. 2016;26:757-763.e2.
210. Grell K, Frederiksen K, Schuz J, Cardis E, Armstrong B, Siemiatycki J, et al. The Intracranial Distribution of Gliomas in Relation to Exposure From Mobile Phones: Analyses From the INTERPHONE Study. *American Journal of Epidemiology*. 2016;184:818-828.
211. Sadetzki S, Turner MC, Figuerola J, ... Parent ML, Richardson L, Siemiatycki J, et al. Occupational exposure to metals and risk for meningioma: a multinational case-control study. *Journal of Neuro-Oncology*. 2016;130(3):505-515.
212. Bigert C, Gustavsson P, Straif K, Taeger D, ..., Siemiatycki J, et al. Lung Cancer Among Firefighters: Smoking-Adjusted Risk Estimates in a Pooled Analysis of Case-Control Studies. *Journal of Occupational Environmental Medicine*. 2016;58(11):1137-43.
213. Zeng F, Lerro C, Lavoué J, Huang H, Siemiatycki J, Zhao N, et al. Occupational exposure to pesticides and other biocides and risk of thyroid cancer. *Occupational Environmental Medicine*. 2017 Feb 15:oemed-2016.
214. Kendzia B, Pesch B, Koppisch D, Van Gelder R, Pitzke K, ... Siemiatycki J, Lavoué J, et al. Modelling of occupational exposure to inhalable nickel compounds. *Journal of Exposure Science and Environmental Epidemiology*. 2017 Jul;27(4):427-433. doi: 10.1038/jes.2016.80.
215. Shareck M, Rousseau MC, Koushik A, Siemiatycki J, Parent ME. Inverse association between dietary intake of selected carotenoids and vitamin C and risk of lung cancer. *Frontiers in Oncology*. 2017Feb 27;7:23 doi: 10.3389/fonc.2017.00023.
216. Olsson AC, Vermeulen R, Schüz J, Kromhout H, Pesch B, ... Siemiatycki J, Parent ME, et al. Exposure-Response Analyses of Asbestos and Lung Cancer Subtypes in a Pooled Analysis of Case-Control Studies. *Epidemiology*. 2017 Mar;28(2):288-299.
217. Oraby T, Sivaganesan S, Bowman JD, Kincl L, Richardson L, McBride M, Siemiatycki J, Cardis E, Krewski D. Berkson error adjustment and other exposure surrogates in occupational case-control studies, with application to the Canadian INTEROCC study. *Journal of Exposure Science and Environmental Epidemiology*, March 29 2017; doi: 10.1038/jes.2017.2. Advance online publication
218. Blanc-Lapierre A, Rousseau MC, Weiss D, El-Zein M, Siemiatycki J, Parent ME. Lifetime report of perceived stress at work and risk of cancer among men: a case-control study in Montréal, Canada. *Preventive Medicine*. 2017 Mar 31;96:28-35.
219. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Patterns and trends in quality of response rate reporting in case-control studies of cancer. *Journal of Epidemiological Research*; 2017 Mar 31;3(2):13.
220. *Ho V, Parent ME, Pintos J, Abrahamowicz M, ... Gauvin L, Siemiatycki J, Koushik A. Physical activity and lung cancer risk in men and women. *Cancer Causes and Control*. 2017 Apr;28(4):309-318.

221. Fehringer G, Brenner DR, ... Siemiatycki J, Koushik A, ... Olsson A, Straif K, Hung RJ, et al. Alcohol and Lung Cancer Risk Among Never Smokers: A Pooled Analysis from the International Lung Cancer Consortium and the SYNERGY Study. *International Journal of Cancer*. 2017 May 1;140(9):1976-1984.
222. Koushik A, Grundy A, ... Mes-Masson AM, Parent MP, Provencher D, Richardson L, Siemiatycki J. Hormonal and reproductive factors and the risk of ovarian cancer. *Cancer Causes Control*. May 2017;28(5):393-403.
223. Auger N, Siemiatycki J, Bilodeau-Bertrand M, Healy-Profítos J, Kosatsky T. Ambient Temperature and Risk of Preeclampsia: Biased association? *Paediatric and Perinatal Epidemiology*. 2017 May 2;31(4):251-384.
224. Turner M, ... Parent M-E, ... Richardson L, Siemiatycki J, et al. Interactions between occupational exposure to extremely low frequency magnetic fields and chemicals for brain tumor risk in the INTEROCC study. *Occupational Environmental Medicine*. 2017 June 9.
225. Ben Khedher S, Neri M, Papadopoulos A, Christiani DC, Diao N, ... Koushik A, Siemiatycki J, et al. Menstrual and reproductive factors and lung cancer risk: a pooled analysis from the International Lung Cancer consortium. *International Journal of Cancer*. 2017 Jul 15;141(2):309-323. doi: 10.1002/ijc.30750.
226. Parent M-É, Turner M, Lavoué J, ... Richardson L, Benke G, ... Siemiatycki J, van Tongeren M, Cardis E. Lifetime occupational exposure to metals and welding fumes, and risk of glioma: a 7-country population-based case-control study. *Environmental Health*. 2017 Aug 25;16(1):90.
227. Benke G, Turner MC, Fleming S, Figuerola J, ... Richardson L, ... Parent ME, Sadetzki S, Siemiatycki J, et al. Occupational solvent exposure and risk of glioma in the INTEROCC study. *British Journal of Cancer*. 2017 Oct 10;117(8):1246-1254. doi: 10.1038/bjc.2017.285.
228. El Zoghbi M, Salameh P, Stücker I, Paris C, Pairon JC, ... Siemiatycki J, ... Lacourt A. Phenotypes of Lung Cancer and Statistical Interactions between Tobacco Smoking and Occupational Exposure to Asbestos and Crystalline Silica from a Large Case-only Study: The CaProMat Study. *Lung Cancer*. 2017;112(Oct):140-155.
229. Momoli F, Siemiatycki J, McBride M, Parent M-É, Richardson L, Bédard D, et al. Probabilistic Multiple-Bias Modelling Applied to the Canadian Data From the Interphone Study of Mobile Phone Use and Risk of Glioma, Meningioma, Acoustic Neuroma, and Parotid Gland Tumors. *American Journal of Epidemiology*. 2017 October;186(7):885-893. doi.org/10.1093/aje/kwx157.
230. El Zoghbi M, Salameh P, Stücker I, Paris C, Pairon JC, ... Siemiatycki J, ... Lacourt A. Prevalence of occupational exposure to asbestos and crystalline silica according to phenotypes of lung cancer from the CaProMat study: A case-only study. *American Journal of Industrial Medicine*. 2018 January;61(1):85-99. 10.1002/ajim.22765.
231. Burstyn I, Gustafson P, Pintos J, Lavoué J, Siemiatycki J. Correction of odds ratios in case-control studies for exposure misclassification with partial knowledge of the degree of agreement among experts who assessed exposures. *Occupational Environmental Medicine*. 2018 Feb(2):155-159. doi: 10.1136/oemed-2017-104609.
232. McElvenny DM, ... Parent ME, ... Richardson L, Siemiatycki J, et al. The INTEROCC case-control study: risk of meningioma and occupational exposure to selected combustion products, dusts and other chemical agents. *Occupational Environmental Medicine*. 2017 December 13;75:12–22.
233. *Xu M, Siemiatycki J, Lavoué J, Pasquet R, Pintos J, Rousseau M.C, Richardson L, Ho V. Occupational exposures to leaded and unleaded gasoline engine emissions and lung cancer risk. *Occupational and Environmental Medicine*. 2018; 75(4):303-309.
234. Hovanec J, Siemiatycki J, Conway DI, Olsson A, Stücker I, Guida F, et al. (2018) Lung cancer and socioeconomic status in a pooled analysis of case-control studies. *PLoS ONE*. 2018 February 20. 13(2): e0192999. doi.org/10.1371/journal.pone.0192999.
235. Behrens T, Hovanec J, Siemiatycki J, et al. 1232 Lung cancer and occupational social status: the synergy study. *Occupational Environmental Medicine*. 2018;75(Suppl 2):A1–A650.
236. *Warden H, Richardson H, Richardson L, Siemiatycki J, Ho V. Associations between occupational exposure to benzene, toluene and xylene and risk of lung cancer in Montréal *Occup Environ Med* Published Online First: 15 May 2018. doi: 10.1136/oemed-2017-104987

237. *Rémen T, Richardson L, Pilorget C, Palmer G, Siemiatycki J, Lavoué J. Development of a coding and crosswalk tool for occupations and industries. *Annals of Work Exposures and Health*. June 15 2018. doi.org/10.1093/annweh/wxy052.
238. *Sauvé JF, Siemiatycki J,... Richardson L, Pintos J,...*Rémen T, *Pasquet R,... Lavoué J. Development of and selected performance characteristics of CANJEM, a general population job exposure matrix based on past expert assessments of exposure. *Annals of Work Exposures and Health*. 12 June 2018. doi.org/10.1093/annweh/wxy044.
239. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Response rates in case-control studies of cancer by era of fieldwork and by characteristics of study design. *Annals of Epidemiology*. 2018 June;28(6):385-391.
240. Wiernik E, Czernichow S,... Limosin F,... Zins M, Siemiatycki J, Goldberg M, et al. Cardiovascular risk goes up as your mood goes down: interaction of depression and socioeconomic status in determination of cardiovascular risk in the CONSTANCES cohort. *International Journal of Cardiology*. 2018 1 July; 262: 99-105.
241. Siemiatycki J & Lavoué J. Availability of a New Job-Exposure Matrix (CANJEM) for Epidemiologic and Occupational Medicine Purposes. *J Occupational Environmental Medicine*. 2018 July;60(7):e324-e328
242. Vila J, Turner M, Gracia-Lavedan E,... Richardson L,... Siemiatycki J, van Tongeren M, Cardis E. Occupational exposure to high-frequency electromagnetic fields and brain tumour risk in the INTEROCC study: An individualized assessment approach. *Environment International*. 2018 October;119:353-365. [Epub ahead of print]
243. Nicolau B, Arekunnath Madathil S, Castonguay G, Rousseau MC, Parent ME, & Siemiatycki J. Shared social mechanisms underlying the risk of nine cancers: A life course study. *International Journal of Cancer*. 2018 July 7.
244. *Lacourt A, Labrèche F, Goldberg M, Siemiatycki J, Lavoué J. Agreement in Occupational Exposures Between Men and Women Using Retrospective Assessments by Expert Coders. *Annals of Work Exposure and Health*. 2018 August 16.
245. Brenner DR, Fehringer G, Zhang ZF,... Siemiatycki J, Koushik A,...Straif K. Alcohol consumption and lung cancer risk: A pooled analysis from the International Lung Cancer Consortium and the SYNERGY study. *Cancer Epidemiology*. 2018. In press.

* First author was under supervision of J. Siemiatycki when this work was carried out.

BOOK CHAPTERS (invited) AND IARC MONOGRAPHS

1. Siemiatycki, J, Gérin M, Hubert J. Exposure-based case control approach to discovering occupational carcinogens: preliminary findings. Banbury Report 9. Quantification of Occupational Cancer. Eds Peto R, Schneiderman M. Cold Spring Harbor, Cold Spring Harbor Laboratory: 471-483, 1981.
2. Siemiatycki, J. Discovering occupational carcinogens with epidemiologic data. In *Chemical Mutagenesis, Human Population Monitoring, and Genetic Risk Assessment*. eds. K. C. Bora, G. R. Douglas and E. R. Nestmann. New York, Elsevier Biomedical Press: 99-105, 1982.
3. Gerin M, Siemiatycki J, Richardson L, Pellerin J, Lakhani R, Dewar R. Nickel and cancer associations from a multicancer occupation exposure case-referent study: preliminary findings. In *Nickel in the Human Environment*. Eds F. W. Sunderman, Jr. Lyon, International Agency for Research on Cancer: 105-115., 1984.
4. Siemiatycki J. An epidemiologic approach to discovering occupational carcinogens by obtaining better information on occupational exposures. In: *Recent Advances in Occupational Health*. Ed. MJ Harrington, Churchill Livingstone Vol. 2, pp. 143-157, 1984.
5. Siemiatycki J. Discovering occupational carcinogens in population-based case-control studies: Review of findings from an exposure-based approach and a methodologic comparison of alternative data collection

- strategies. In: Occupational Cancer Epidemiology, Ed. P Band, Springer-Verlag Press. Berlin. 25-38, 1990.
6. Krewski, D, Siemiatycki J, Nadon L, Dewar R, and Gérin M. Cancer risks due to occupational exposure to polycyclic aromatic hydrocarbons: a preliminary report. In Genetic Toxicology of Complex Mixtures. Eds M.D. Waters, F.B. Daniel, J.Lewtas, M.M. Moore and S. Newnow. New York, Plenum Press: 343-352, 1990.
 7. Siemiatycki, J., M. Gérin, R. Dewar, R. Lakhani, D. Bégin and L. Richardson. Silica and cancer associations from a multicancer occupational exposure case-referent study. In Occupational Exposure to Silica and Cancer Risk. Eds L. Simonato, A. C. Fletcher, R. Saracci and T. L. Thomas. Lyon, International Agency for Research on Cancer: 29-42, 1990.
 8. IARC Working Group (21 co-authors) (1991). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 52. Chlorinated drinking-water; chlorination by-products; some other halogenated compounds; cobalt and cobalt compounds. Lyon, IARC (International Agency for Research on Cancer).
 9. Siemiatycki, J. Risk factors for cancer in the occupational environment and relevant epidemiologic study methods. In Introduction to Environmental Epidemiology. Eds E. Talbott and G. Craun. Boca Raton, Lewis Publishers: 99-122, 1995.
 10. IARC Working Group (17 co-authors) (1996). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 65. Printing processes and printing inks, carbon black and some nitro compounds. Lyon, IARC (International Agency for Research on Cancer).
 11. Siemiatycki J. Job-exposure matrices. In: Encyclopedia of Biostatistics, eds. P Armitage and T Colton. Wiley, 1998.
 12. Siemiatycki J. Job-exposure matrices. In: Encyclopedia of Epidemiologic Methods, eds. MH Gail and J Benichou. Wiley, 2000.
 13. Siemiatycki J, Richardson L, Boffetta P. Occupation. In: Cancer Epidemiology and Prevention, 3rd Ed, eds. D Schottenfeld and J Fraumeni, Oxford University Press, 2006.
 14. IARC Monograph Working Group. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 93 - Carbon black, titanium dioxide and non-asbestiform talc, IARC (International Agency for Research on Cancer), Lyon, 2009.
 15. Siemiatycki J. Les règles, les pratiques et les préjugés des comités d'éthique vont réduire notre capacité à prévenir les maladies et à sauver des vies in La malréglementation, Une éthique de la recherche est-elle possible et à quelles conditions? Sous la direction de Michèle S. Jean et Pierre Trudel. Les Presses de l'Université de Montréal 2010.
 16. IARC (2010). IARC Technical Publication No. 42: Identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens.
<http://monographs.iarc.fr/ENG/Publications/techrep42/index.php>
 17. IARC Monograph Working Group. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 100 – A review of human carcinogens, part C: metals, arsenic, dusts and fibres, IARC (International Agency for Research on Cancer), Lyon, 2012.
 18. IARC Monograph Working Group. IARC Monographs on Evaluation of Carcinogenic Risks to Humans Vol. 102 – Radio Frequency Fields 2011, IARC (International Agency for Research on Cancer), Lyon, 2013.
 19. Siemiatycki J. Occupational exposures, Chapter 2.6. In IARC World Cancer Report. Eds B Stewart, C Wild. Lyon 2013.
 20. Siemiatycki J. Historical overview of occupational cancer research and control. In Occupational Cancers. Eds S Anttila, P Boffetta, K Straif. Springer Press: 1-20, 2014.

PUBLICATIONS WITHOUT PEER REVIEW, OTHER SCIENTIFIC REPORTS

1. Rossiter CE, Bristol LJ, Cartier PH, Gibbs GW, Gilson JC, Grainger TR, Siemiatycki J, Sluis-Cremer GK, McDonald JC. Dust exposure and radiographic appearances in Quebec asbestos workers. XVI International Congress on Occupational Health, Tokyo: 205-206, 1969.
2. Siemiatycki J. Living conditions and health - with special reference to low income areas of Montréal. Report submitted to the Pointe St-Charles Community Clinic, 42 pp, 1972.

3. Siemiatycki J. The distribution of disease. Canadian Dimension. 1975.
4. Siemiatycki J, Richardson L. Les facteurs socio-économiques et l'utilisation des services de santé à Montréal: document de travail. Submitted to the Ministère des Affaires sociales, 1979.
5. Siemiatycki J, Richardson L. Les corrélatifs sociaux de la morbidité tels qu'ils ressortent d'une enquête sur la santé menée à Montréal: rapport préliminaire. Submitted to the Ministère des Affaires sociales, 1979.
6. Siemiatycki J. Les facteurs qui déterminent la consommation de médicaments obtenus par prescription et les facteurs associés aux affections chroniques: rapport préliminaire. Submitted to the Ministère des Affaires sociales, 1979.
7. Groupe d'étude de la fonction épidémiologique. (Aubry F, Drouin L, Ducharme G, Fredette JM, Lance JM, Siemiatycki J.) La fonction épidémiologique à la Commission de Santé et Sécurité au travail. Submitted to the Direction des Programmes et Normes, Commission de Santé et Sécurité au Travail, Québec, 1980.
8. Siemiatycki J. An exposure-based case-control method for discovering occupational carcinogens. Chronic Diseases in Canada, 1:21-24, 1980.
9. Siemiatycki J, Richardson L. Les corrélatifs sociaux de la morbidité tels qu'ils ressortent d'une enquête sur la santé à Montréal. Submitted to the Ministère des Affaires Sociales, 1981.
10. Siemiatycki J. La consommation de médicaments à Montréal selon les facteurs démographiques, économiques, et ethniques. Submitted to the Ministère des Affaires Sociales, 1981.
11. Siemiatycki J. Mortality in the general population in asbestos mining areas. Proceedings of the World Symposium on Asbestos, Montréal, 337-348, 1982.
12. Price P, Gerin M, Siemiatycki J. An annotated bibliography of sources of information on occupational exposures. pp.78, 1982.
13. Gerin M, Siemiatycki J, Kemper H, Laroche L, Millet C. Translating job histories into histories of occupational exposure for epidemiologic purpose. Proceedings of the Medical Research Council Symposium on Job Exposure Matrices, Southampton, Scientific Report No 2, 78-82, 1983.
14. Siemiatycki J, Gerin M, Nadon L, Goldberg M, Richardson L. L'exposition professionnelle au formaldéhyde et le risque de cancer. Submitted to the Institut de recherche en santé et sécurité du travail, 18 pp, 1983.
15. Task Force on Chemicals in the Environment and Human Reproductive Problems in New Brunswick. Second Report. Submitted to the Department of Health of New Brunswick. 249 pp, January 1984.
16. Siemiatycki J. Evaluation des estimations actuelles concernant l'exposition professionnelle aux cancérrogènes chimiques. Submitted to the Commission de la santé et sécurité au travail du Québec, 87 pages. October 1984.
17. Task Force on Chemicals in the Environment and Human Reproductive Problems in New Brunswick. Final Report submitted to the Department of Health of New Brunswick. 269 pp, March 1985.
18. Siemiatycki J, Richardson L. Expanding the vision of public health: new ways to meet old objectives. Health Promotion 24(2):10-12, 1985.
19. Task Force on Health Risks of Alachlor (A.J. Nantel, J.L. Benedetti, J.P. Farand, M. Pagé, J.C. Panisset, J. Siemiatycki, C. Viau). Report submitted to the Government of Quebec, 1986.
20. Siemiatycki J. Determining which workplace exposures may be carcinogenic: report on a novel epidemiologic approach. At The Centre. Canadian Centre for Occupational Health and Safety. Vol. IX, no. 5, pp. 9-10, November 1986.
21. Gerin M, Siemiatycki J. Assessment of exposure to multiple agents in the workplace. Proceedings of the Workshop on Methodology of Assessment of Occupational Exposures in the Context of Epidemiological Detection of Cancer Risks. Eds. D. Hemon, M. Goldberg, pp. 99-108, 1989.
22. Siemiatycki J, Gerin M, Nadon L, Dewar R. Risk of cancer due to occupational exposure to formaldehyde in a wide range of occupations and industries. Final report. Submitted under contract no. 1674 to the Health Protection Branch, Health and Welfare Canada, 78 pages, May 1988.
23. Siemiatycki J. Epidemiological evidence in evaluating carcinogenicity of occupational exposures. IARC Int. Tech. Report no. 88/002, IARC, Lyon, Dec, pp. 49-59, 1988.

24. IARC Working Group. Report of an IARC Working Group to review the approaches and processes used to evaluate the carcinogenicity of mixtures and groups of chemicals. IARC Int. Tech. Report no. 88/002, IARC, Lyon, Dec. 1988.
25. Siemiatycki J, Nadon L, Dewar R, Gerin M, Armstrong B, Richardson L. Risk of cancer due to occupational exposure to polynuclear aromatic hydrocarbons in a wide range of occupations and industries: Final report. Submitted under contract no. 1984 to the Health Protection Branch, Health and Welfare Canada, 162 pages, May 1989.
26. Siemiatycki J, Lakhani R, Gerin M, Dewar R, Richardson L. Risk of cancer due to exposure to benzene, toluene, and xylene in a wide range of occupations and industries: Final report. Submitted under contract no. 2025 to the Health Protection Branch, Health and Welfare Canada, 235 pages, June 1989.
27. Siemiatycki J, Franco E, Dewar R, Desy M. Risk of cancer due to cigarette smoking - results of a multi-site case-control study. Report submitted under contract no. 2069 to the Health Protection Branch, Health and Welfare Canada, 23 pages, March 1990.
28. Siemiatycki J. Review of findings from a registry-like database designed to discover occupational carcinogens. Proceedings of the Workshop on Indicators of Environmental Health. Waterloo Institute for Risk Research and Health and Welfare Canada. 1990.
29. Camus M, Siemiatycki J. Cancer risks associated with non-occupational exposure to chrysotile asbestos. Report submitted under contract no. 064SS.H4078-1-C339. 1991.
30. Siemiatycki J. Toxic Waste Sites And Human Health: Feasibility of Epidemiologic Studies Using the Canadian Unified Toxic Waste Sites Database. Contract No. 3136. 1992.
31. *Nadon L, Siemiatycki J, Richardson L. Dépistage épidémiologique de cancérogènes en milieu de travail et son implication sur la santé environnementale. Bulletin d'Information en Santé environnementale, Volume 4, number 3, May/June 1993.
32. Gerin M, deGuire L, Siemiatycki J. Étude sur la validité des matrices emploi-exposition multisectorielles en hygiène industrielle. IRSST, Montréal, 1995.
33. Goldberg M, Farant JP, Simon P, Siemiatycki J, Armstrong B, Drouin L. A health survey of persons living near the Miron Quarry Sanitary Landfill Site. Montréal, Phase 1 (NHRDP: 502-6605-4342). July 1996.
34. Siemiatycki J, Camus M, Case BW. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer. Montréal, NHRDP Report No. 6605-3533-53. April 1996.
35. Mills CJ, Bull R, Cantor KP, Reif J, Hrudey SE, Huston P and an Expert Working Group: Health risks of drinking water chlorination byproducts: report of an expert working group. Chronic Diseases in Canada. 1998.
36. Krewski D, Burnett R, Goldberg M, Hoover K, Siemiatycki J, et al. Reanalysis of the Harvard Six-City Study and the American Cancer Society Study of Air Pollution and Mortality: Validation and Replication. Health Effects Institute, Cambridge MA, 2000.
37. Krewski D, Burnett R, Goldberg M, Hoover K, Siemiatycki J, et al. Reanalysis of the Harvard Six-City Study and the American Cancer Society Study of Air Pollution and Mortality: Sensitivity Analyses. Health Effects Institute, Cambridge MA, 2000.
38. Payment J, Siemiatycki J, Richardson L, Renaud G, Franco E, Prevost M. An epidemiological study of gastrointestinal health effects of drinking water. American Water Works Assoc. 103 pp. 2000.
39. Raynault M-F, Dussault C, Bartlett G, Deschenes M, Fortin S, Giroux M, Godard B, Jean MS, Mes-Masson A-M, Siemiatycki J, Vachon M-H. Rapport final du groupe-conseil sur l'Encadrement des banques de données et des banques de matériel biologique à des fins de recherche en santé. Fonds de la recherche en santé du Québec (FRSQ), Montréal, Québec. 8 December 2006.
40. Raynault M-F, Dussault C, Bartlett G, Deschenes M, Fortin S, Giroux M, Godard B, Jean MS, Mes-Masson A-M, Siemiatycki J, Vachon M-H. Sommaire du rapport final du groupe-conseil sur l'Encadrement des banques de données et des banques de matériel biologique à des fins de recherche en santé. Fonds de la recherche en santé du Québec (FRSQ), Montréal, Québec. 8 December 2006.
41. Raynault M-F, Dussault C, Bartlett G, Deschenes M, Fortin S, Giroux M, Godard B, Jean MS, Mes-Masson A-M, Siemiatycki J, Vachon M-H. Reconnaître la valeur sociale de la recherche dans le respect

de la personne : Banques de données et banques de matériel biologique - Pour un nouveau cadre éthique et légal. Fonds de la recherche en santé du Québec (FRSQ), Montréal, Quebec. May 2007.

42. Siemiatycki J. Estimating the amount of environmental health research being funded by national funding agencies in Canada. Report submitted under contract no. 4500156045 to Health Canada (Environmental and Occupational Toxicology & Environmental Health Sciences Bureau), 40 pages. August 2007.

BOOK

1. Siemiatycki J. Risk Factors for Cancer in the Workplace. CRC Press, Boca Raton, 1991, 310 pp.
Chap 1. Siemiatycki J. Epidemiologic approaches to discovering occupational carcinogens
Chap 2. Siemiatycki J, Richardson L. Case-control design and fieldwork methods.
Chap 3. Siemiatycki J. Nadon L, Lakhani R, Begin D, Gerin M. Exposure assessment.
Chap 4. Siemiatycki J. Statistical methods.
Chap 5. Siemiatycki J, Gérin M, Dewar R, Nadon L, Lakhani R, Begin D, Richardson L. Associations between occupational circumstances and cancer
Chap 6. Siemiatycki J. Interpretation of findings.

ARTISTIC WORKS

1. Siemiatycki J, Slodovnick A. The Hockey Card. Illustrated by Doris Barrette. Lobster Press, Montréal, 2002, 32 pp.
2. Siemiatycki J, Slodovnick A. La carte de hockey. Illustrated by Doris Barrette. Translated by Christiane Duchesne. Lobster Press, Montréal, 2002, 32 pp.
3. Siemiatycki J, Slodovnick A. The Baseball Card. Illustrated by Laura Watson. Lobster Press, Montréal, 2005, 32 pp.
4. Siemiatycki J, Slodovnick A. La Estampa de béisbol. Illustrated by Laura Watson. Translated. Lobster Press, Montréal, 2005, 32 pp.

SCIENTIFIC PRESENTATIONS - INVITED

1. Siemiatycki J. Monitoring the occupational environment for carcinogens: a pilot study in Montréal. Working Environment and Health Seminar, McGill University, Department of Epidemiology, September 1978.
2. Siemiatycki J, Richardson L. Le défi prioritaire en santé communautaire: la protection et l'amélioration de l'environnement. Association pour la santé publique du Québec, Montréal, Quebec, October 1979.
3. Siemiatycki J. Occupational carcinogenesis. Séminaire départemental, Direction générale de la protection de la santé, Santé et Bien-être Social Canada, Ottawa, January 1981.
4. Siemiatycki J. An overview of problems in identifying occupational carcinogens. Canadian Labour Congress Meeting on Occupational Cancer, Montréal, February 1981.
5. Siemiatycki J. Feasibility of an exposure-based case-control approach to discovering occupational carcinogens: preliminary findings. Cold Springs Harbor Conference on Quantification of Occupational Cancer, Cold Springs Harbor, New York, March 1981.
6. Siemiatycki J. Dépistage des facteurs cancérigènes dans les milieux professionnels montréalais. Séminaire départemental, Département de médecine du travail et d'hygiène du milieu, Université de Montréal, Montréal, Quebec, March 1981.
7. Siemiatycki J. Surveillance program for occupationally related cancer. Société de Toxicologie du Canada, Montréal, Quebec, December 1981.
8. Gérin, J, Siemiatycki J. Translating job histories into histories of occupational exposure in an interview-based case-control Study. Medical Research Council Symposium on Job-Exposure Matrices, Southampton, England, April 1982.
9. Siemiatycki J. Rapporteur's report. Medical Research Council Symposium on Job-Exposure Matrices, Southampton, England, April 1982.
10. Siemiatycki J. Mortality in the general population in Quebec's asbestos mining areas. World Symposium on Asbestos, Montréal, May 1982.

11. Siemiatycki J. Occupational cancer epidemiology. McGill Department of Epidemiology seminar series, Montréal, Quebec, October 1982.
12. Siemiatycki J. Rapport d'une étude pilote qui vise à découvrir des agents cancérigènes de l'environnement professionnel. Institut Armand-Frappier, Laval, Quebec, October 1982.
13. Siemiatycki J, Richardson L, Gérin M. Discovering occupational carcinogens by an exposure-based case-control approach: feasibility and pilot study results. American Public Health Association Meeting, Montréal, Quebec, November 1982.
14. Siemiatycki J. Discovering occupational carcinogens by means of a novel exposure-based case-control approach. U.S. National Institute of Occupational Safety and Health seminar series. Cincinnati. November 1982.
15. Siemiatycki J. Dépistage des facteurs cancérigènes dans le milieu professionnel montréalais - rapport d'une étude pilote. Conférence-midi de l'Institut de recherche en santé et sécurité au travail, Montréal, Quebec, December 1982.
16. Siemiatycki J. Rapport d'une étude qui vise à découvrir des agents cancérigènes dans l'environnement professionnel. Conférence départementale, Université de Sherbrooke, Sherbrooke, Quebec, February 1983.
17. Siemiatycki J. Contribution of epidemiology to discovery of occupational carcinogens: case-control study in the Montréal area. Seminar Series, Lady Davis Institute, Jewish General Hospital, Montréal, March 1983.
18. Siemiatycki J. Hospital-based studies of environmental causes of cancer. Seminar series, McGill Cancer Centre and Montréal General Hospital, March 1983.
19. Siemiatycki J. Analyse préliminaire d'une enquête cas-témoins sur les expositions professionnelles et le cancer, INRS-Santé, Paris, France, April 1983.
20. Siemiatycki J. Découvrir les cancérigènes professionnels par des méthodes épidémiologiques. Congrès de l'ACFAS, Trois-Rivières, Quebec, May 1983.
21. Siemiatycki J. Surveillance of occupational cancer. University of Ottawa Special Course in Environmental Epidemiology, Ottawa, October 1983.
22. Gérin M, Richardson L, Siemiatycki J. Obtaining job exposure histories based on interview and expert assessment. Job Exposure Assessment Meeting. International Agency for Research on Cancer, Lyon, France, February 1984.
23. Siemiatycki J. Associations between bladder cancer and coffee and cigarette consumption: preliminary results of a case-control study. Environmental Risk Factors in Bladder Cancer Symposium, Lyon, February 1984.
24. Siemiatycki J. Preliminary results of an occupational cancer monitoring program. Kellogg Center Seminar Series. Montréal General Hospital, April 1984.
25. Siemiatycki J. Nickel, chromium and cancer: preliminary results from a case-control study. School of Occupational Health. McGill University, Montréal, April 1984.
26. Siemiatycki J. Les premiers résultats d'une stratégie épidémiologique visant à découvrir des produits cancérigènes dans l'environnement industriel. Micro-hebdo, Institut Armand-Frappier, May 1984.
27. Siemiatycki J. Cancer mortality in a general population highly exposed to asbestos. CAN-AM Chemical Congress. Montréal, June 1984.
28. Siemiatycki J. Some occupational and non-occupational risk factors for cancer: results from a multi-site case-control study in Montréal. Special seminar. Health Protection Branch of Health and Welfare Canada, January 1985.
29. Siemiatycki J. Premiers résultats d'un système de surveillance en épidémiologie visant à découvrir des agents cancérigènes dans le milieu industriel. Micro-Hebdo-Actualités, Institut Armand-Frappier, Laval, February 1985.
30. Siemiatycki J. Discovering environmental carcinogens. Elizabeth Stern Memorial Lecture. U.C.L.A. School of Public Health, Los Angeles, California, May 1985.
31. Siemiatycki J. Cancer surveillance. International Conference on Environmental and Occupational Significance of Industrial Carcinogens, Bologna, Italy, October 1985.

32. Siemiatycki J. Overview of an epidemiologic case-control approach to discovering occupational carcinogens. Special seminar. Health Department of Torino and Epidemiology Department of University of Torino, Torino, Italy, October 1985.
33. Siemiatycki J. Epidemiology of juvenile-onset diabetes in Montréal. Special lecture to Association of endocrinologists of Rhone-Alpes Region of France, Lyon, October 1985.
34. Siemiatycki J. Cancer risks associated with exposure to organic dusts. Special seminar. International Agency for Research on Cancer, Lyon, October 1985.
35. Siemiatycki J. Organic dusts and cancer. School of Occupational Health Seminar Series, McGill University, December 1985.
36. Gérin, M, Siemiatycki J, Richardson L, Begin, D, Kemper, H, Lakhani, R, Nadon L. Associations entre cancer et exposition professionnelle à diverses substances. Résultats d'une étude épidémiologique à Montréal. Association pour l'hygiène industrielle au Québec, VIII Congrès, City of Québec, Quebec, May 1986.
37. Siemiatycki J. Synthèse des résultats d'un système de surveillance épidémiologique des expositions professionnelles cancérigènes, Université Laval, May 1986.
38. Siemiatycki J. L'analyse des données appliquée à la santé et à la sécurité du travail. Symposium sur l'analyse de données, IRSST, Montréal, October 1986.
39. Siemiatycki J. An overview of epidemiologic contributions to the discovery of occupational carcinogens. Society of Toxicology of Canada, Montréal. December 1986.
40. Siemiatycki J, Wacholder, S, Dewar R, Begin, D, Richardson L, Rosenman, K, Gerin M. Smoking and degree of occupational exposure: are internal analyses likely to be confounded by smoking status? Symposium on Smoking in Occupational Cancer Studies. National Cancer Institute, Washington, December 1986.
41. Siemiatycki J. Petroleum-derived liquids and cancer risk: findings from a case-control study. McGill University, Department of Epidemiology, April 1987.
42. Siemiatycki J. Methods and findings from a case-control study of insulin-dependent diabetes mellitus in Montréal. Montréal Children's Hospital, May 1987.
43. Colle, E, Siemiatycki J. Epidemiologic and immunologic evidence concerning the etiology of insulin-dependent diabetes. Institut Armand-Frappier, May 1987.
44. Siemiatycki J. The role of epidemiology in environmental impact assessment. Symposium on Health in Environmental Impact Assessment. Canadian Public Health Association and Environment Canada, Ottawa, May 1987.
45. Siemiatycki J. Methods and results of a monitoring system for occupational carcinogens. Johns Hopkins University School of Public Health Seminar, Baltimore, Maryland, October 1987.
46. Siemiatycki J. Cancer risks associated with petroleum-derived liquids and combustion products. National Cancer Institute, Occupational Studies Section, Bethesda, Maryland, October 1987.
47. Gerin M, Siemiatycki J. Assessment of exposure to multiple agents in the workplace - experience from a population-based case-control study in Montréal. Workshop of European Economic Community on Methods of Assessment of Occupational Exposures for Epidemiologic Detection of Cancer Risks, Paris, February 1988.
48. Siemiatycki J. Overview of epidemiologic tasks. International Joint Commission Workshop on the Role of Epidemiology in Assessing the Effects of Great Lakes Water Quality on Human Health. Toronto, March 1988.
49. Siemiatycki J. Results of an exposure-based case-control study of occupational carcinogens. Ontario Cancer Treatment and Research Foundation, Toronto, April 1988.
50. Siemiatycki J. Methodology of cancer case-control studies. Special Lecture Series in McGill Summer Program in Epidemiology, Montréal, May 1988.
51. Siemiatycki J. Costs and benefits of various approaches to estimating occupational cancer risks in case-control studies. Symposium on Occupational Cancer Epidemiology. Vancouver, June 1988.
52. Richardson L.R, Siemiatycki J, Dewar R. How well does a job exposure matrix reflect the exposure assessment of individually coded job histories? Workshop on job exposure matrices held at INSERM, Paris, October 1988.

53. Siemiatycki J. Methodologic issues in an exposure-based case-control study for discovering occupational carcinogens. Medical Research Council, Biostatistics Unit, Cambridge, England, December 1988.
54. Siemiatycki J. A synthesis of findings from an occupational cancer case-control study. Invited seminar in Department of Epidemiology, School of Public Health, University of North Carolina. Chapel Hill, North Carolina, April 1989.
55. Siemiatycki J. Methodologic problems in assessing exposure status for case-control studies. National Cancer Institute Seminar, Silver Spring, Maryland. April 1989.
56. Siemiatycki J. Environmental causes of cancer. McGill Cancer Center Public Lecture Series, Montréal. May 1989.
57. Siemiatycki J. Approches épidémiologiques dans l'investigation des facteurs cancérigènes. Summer course in community health, Université Laval, City of Québec, Quebec, June 1989.
58. Krewski, D, Siemiatycki J, Nadon L, Dewar R, Gerin M. Cancer risks due to occupational exposure to PAH's. International Conference on Genetic Toxicology of Complex Mixtures, Washington, District of Columbia, September 1989.
59. Siemiatycki J. Discovering environmental carcinogens by means of a case-control methodology. Dalhousie University, Faculty of Medicine seminar, December 1989.
60. Siemiatycki J. Using epidemiologic evidence in compensation of industrial disease. Special workshop of Industrial Disease Standards Panel of Ontario, Toronto, December 1989.
61. Siemiatycki J. Epidemiologic approaches to evaluating the carcinogenicity of complex mixtures. Workshop on carcinogenicity of Complex Mixtures. National Academy of Sciences of the U.S.A., Tucson, January 1990.
62. Siemiatycki J. Review of findings from a registry-like database designed to discover occupational carcinogens. Workshop on Indicators of Environmental Health. Waterloo Institute for Risk Research and Health and Welfare Canada, Ottawa, March 1990.
63. Siemiatycki J. Findings from an occupational cancer case-control study. Invited seminar in Department of Clinical Epidemiology, Royal Victoria Hospital. Montréal, March 1990.
64. Siemiatycki J. Effect of exposure strategies on risk estimates and statistical power. International Workshop on Retrospective Exposure Assessment for Occupational Epidemiologic Studies, Leesburg, Virginia, March 1990.
65. Siemiatycki J. Discovering environmental carcinogens: an epidemiologic perspective. Invited seminar in Department of Epidemiology, School of Public Health, University of North Carolina. Chapel Hill, North Carolina, March 1990.
66. Siemiatycki J. Discovering environmental carcinogens: review of an epidemiologic surveillance project. Invited seminar in Occupational & Environmental Health Unit, University of Toronto, Toronto, April 1990.
67. Siemiatycki J. Environnement et cancer: une perspective épidémiologique. 58th Association canadienne française pour l'avancement des sciences. Colloque santé et environnement, City of Québec, Quebec, April 1990.
68. Payment P, Richardson L, Edwards M, Franco E, Siemiatycki J. Drinking water related illness: an epidemiological study. Second International Biennial Water Quality Symposium: Microbiological Aspects, Vina Del Mar, Chile, August 1990.
69. Siemiatycki J. Occupational cancer. Seminar series of Laboratory Centre for Disease Control, Health and Welfare Canada, Ottawa, March 1991.
70. Siemiatycki J. A decade of searching for occupational carcinogens: methods and results of a case-control study. Seminar series of the Division of Clinical Epidemiology, Montréal General Hospital, Montréal, March 1991.
71. Siemiatycki J. Detecting occupational carcinogens using epidemiologic methods: results and their interpretation. McGill University, Department of Epidemiology and Biostatistics, Summer Lecture Series, Montréal, June 1991.
72. Siemiatycki J. Overview of results of an occupational cancer monitoring study. School of Public Health, University of California at Berkeley, Berkeley, October 1991.

73. Siemiatycki J. Discussant of paper on Mortality of oil refinery and distribution workers. International Symposium on the Health Effects of Gasoline, Miami, November 1991.
74. Begin, D, Gerin M, De Guire L, Siemiatycki J, Adib G, Fournier C. Étude sur la validité des matrices emploi-exposition multisectorielles en hygiène industrielle. Scientific Committee on Computing in Occupational and Environmental Health, III International Workshop, Paris, November 1991.
75. Siemiatycki J. Cancer et travail : connaissances actuelles, approches antérieures et nouvelles. Colloque de l'Association des médecins du travail du Québec, Montréal. June 1992.
76. Siemiatycki J. Risques de cancers reliés aux expositions chimiques en milieu de travail: résultats d'une étude épidémiologique à Montréal. IRSST, Montréal, November 1992.
77. Siemiatycki J. Carcinogens in the occupational environment. Invited seminar in School of Public Health, University of North Carolina, Chapel Hill, North Carolina. December 1992.
78. Siemiatycki J. Discussant of invited seminar on risk assessment. School of Occupation Health, McGill University, March 1993.
79. Siemiatycki J. Are the effects of smoking on lung and bladder cancer confounded by occupational carcinogens? Invited seminar given at the Michigan Cancer Foundation, Detroit and at the University of Michigan, Ann Arbor, May 1993.
80. Siemiatycki J. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? McGill University, Department of Epidemiology and Biostatistics, Montréal, December, 1993.
81. Siemiatycki J. Occupational causes of cancer. President's Cancer Panel Meeting on Avoidable Causes of Cancer, Bethesda, April 1994.
82. Siemiatycki J. Retrospective exposure assessment in community-based studies. Conference on Retrospective assessment of occupational exposures in epidemiology, IARC, Lyon, April 1994.
83. Siemiatycki J. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? Department of Human Oncology, University of Torino, Torino, Italy, April 1994.
84. Siemiatycki J. Risque de cancer dû au tabagisme. Département de médecine sociale et préventive, Université Laval, Québec, May 1994.
85. Siemiatycki J. Registry studies of bladder cancer. NCI Workshop on Occupational Exposures and Urogenital Cancers, Rockville, May 1994.
86. Siemiatycki J. Facteurs de risques environnementaux pour le cancer: une perspective épidémiologique. Atelier sur la recherche en cancer, Université du Québec à Rimouski, April 1995.
87. Camus M, Siemiatycki J. Non-occupational exposure to asbestos: how to assess dose and risk. McGill University, Department of Epidemiology and Biostatistics. Montréal, May 1995.
88. Siemiatycki J. Occupational carcinogens in Montréal. Seminar - International Agency for Research on Cancer, Lyon, France, June 1995.
89. Siemiatycki J. Occupational causes of cancer: findings from a large scale case-control study of occupational cancer. Department of Medical Informatics, Biometry and Epidemiology, University of Essen, Essen, Germany, July 1995.
90. Siemiatycki J. Assessing occupational exposures in community based epidemiological studies. Bremen Institute for Preventive and Social Medicine, Bremen, Germany, July 1995.
91. Case, B, Camus M, Richardson L, Siemiatycki J. Ascertainment of mesothelioma among Québec women from 1970 to 1990. Special Symposium on Mesothelioma, IRSST, Montréal, August 1995.
92. Siemiatycki, J. Une nouvelle approche épidémiologique pour le dépistage de cancérrogènes en milieu de travail. Club de recherches cliniques du Québec, Bromont, Quebec, September 1995.
93. Siemiatycki J. Occupational causes of cancer: findings from a large scale case-control study of occupational cancer. Special seminar. School of Public Health, Univ. of Michigan, Ann Arbor, Michigan, June 1996.
94. Siemiatycki J. An empirical evaluation of the magnitude of confounding bias. Statistical Society of Canada, Waterloo, June 1996.

95. Siemiatycki J. Occupational exposures and cancer risk: recent results and methodological insights from a population-based case-control study in Montréal. Department of Epidemiology & Biostatistics, McGill University. October, 1996.
96. Siemiatycki J. Utilités et limites des études épidémiologiques dans l'évaluation des risques environnementaux. ACFAS, City of Québec, Quebec, May 1998.
97. Siemiatycki J. International collaboration in cancer epidemiology. Society for Epidemiology Research, Chicago, June 1998.
98. Siemiatycki J. Accuracy of the EPA risk assessment model for predicting the risk of lung cancer at environmental levels of asbestos exposure. National Cancer Institute, Rockville, Maryland, March 1999.
99. Siemiatycki J. Risk of lung cancer at environmental levels of asbestos exposure. University of Toronto, Toronto, September 1999.
100. Siemiatycki J. Estimating risks due to low level exposures. Society for Epidemiology Research, Seattle, June 2000.
101. Siemiatycki J. Debater on the proposition that research is a top priority in occupational cancer prevention. Preventive Oncology Seminar, Cancer Care Ontario, Toronto, April 2001.
102. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondre K. Various aspects of smoking behavior on lung cancer risk: a flexible modeling approach. National Cancer Institute, Bethesda, May 2001.
103. Siemiatycki J. Challenges to epidemiology and challenges to Canadian epidemiologists. National Student Conference of Epidemiology, Toronto, June, 2001.
104. Siemiatycki J. President's address. Congress of Epidemiology, Toronto, June, 2001.
105. Siemiatycki J. Découvrir les cancérigènes dans l'environnement: bilan des activités de recherche passées et perspectives d'avenir. Département de médecine sociale et préventive, Université de Montréal, October 2001.
106. Siemiatycki J. Risque de cancer chez les femmes résidentes des villes des mines d'amianté québécoises: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque (« risk assessment ») du E.P.A. Département de santé environnementale, Université de Montréal, October 2001.
107. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Relations dose-réponse entre la fumée de cigarette et le cancer pulmonaire à partir d'une étude cas-témoins à Montréal : Estimations utilisant une modélisation flexible. Congrès INRS-Institut Armand-Frappier, Sainte-Adèle, Quebec, November 2001.
108. Siemiatycki J, Camus M, Case B, Desy M, Parent, M.-É. Risque de cancer chez les résidentes des villes de l'amianté au Québec: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque de l'E.P.A. Symposium sur l'amianté of Institut national de santé publique du Québec, Montréal, December 2001.
109. Laplante O, Parent M.-É, Siemiatycki J. Risque de mésothéliome et de cancer du poumon associé à l'exposition professionnelle aux fibres d'amianté, Montréal 1979-85. Symposium de l'Institut national de santé publique du Québec, Montréal, December 2001.
110. Siemiatycki J. Occupational causes of cancer: overview of the contribution of a study in Montréal, Research Day at Dept of Epidemiology and Community Medicine, University of Ottawa, April 2002.
111. Siemiatycki J. Biostatistical problems in epidemiologic case-control studies. Statistical Society of Canada, Hamilton, Ontario, May 2002.
112. Leffondre K, Abrahamowicz M, Siemiatycki J. Definition of risk sets for Cox's analysis of case-control data with time-varying exposures: A simulation study. Intended Society for Clinical Biostatistics (ISCB), Dijon, France, September 2002.
113. Siemiatycki J. Occupational causes of cancer. CCERN and Health Canada Research Workshop, Montebello, Quebec. October 2002.
114. Siemiatycki J. Occupational causes of cancer. Departmental seminar, McGill University, Montréal. November 2002.
115. Siemiatycki J. Facteurs environnementaux dans l'étiologie du cancer. Retraite annuelle du centre de recherche du CHUM, St-Sauveur, Quebec. November 2002.
116. Siemiatycki J. Environmental and occupational causes of cancer. Seminar. Cancer Care Ontario, Toronto, February 2003.

117. Siemiatycki J. The state of epidemiology in Canada. Plenary address. CSEB Student Congress, Halifax, Nova Scotia, June 2003.
118. Siemiatycki J. Occupational cancer epidemiology: the evolving big picture. Distinguished Scientist Lecture, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville MD, October 2003.
119. Siemiatycki J. Challenges in cancer epidemiology. Meeting of the Institute Advisory Board of Institute for Cancer Research, CIHR, Montréal, June 2004.
120. Siemiatycki J. Keynote address. Occupation and cancer. International Association of Cancer Registries, Beijing, September 2004.
121. Siemiatycki J. Which cancers are most important, what are the associated occupational situations and which confounders are involved? Burden of Cancer Epidemiologic Workshops, Health and Safety Executive. Manchester, UK, November 2004.
122. Siemiatycki J. Occupational causes of cancer. New Strategies for Recognizing and Preventing Occupational Disease, Canadian Center for Occupational Health and Safety, Toronto, March 2005.
123. Siemiatycki J. Occupational causes of cancer. The Respiratory Epidemiology & Clinical Research Unit, Montréal Chest Institute, Montréal, March 2005.
124. Siemiatycki J. Environnement et cancer : quels sont les risques? Les Belles Soirées public lecture series, Université de Montréal, Montréal, April 2005.
125. Siemiatycki J. An overview of environmental, occupational & lifestyle causes of lung cancer. Cancer Axis, McGill University Hospital Centre Research Institute, Montréal, June 2005.
126. Siemiatycki J. Les règles des comités d'éthique vont amputer notre capacité de prévenir des maladies et sauver des vies. Réunion de FRSQ sur les banques de données et des matières biologiques, Montréal, June 2005.
127. Siemiatycki J. Introductory comments. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
128. Siemiatycki J. The burden of occupational cancer on workers and on society. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
129. Siemiatycki J. Revue des expositions professionnelles associées au cancer (Review of occupational exposures associated with cancer): pre-conference training session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
130. Siemiatycki J. Opening session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
131. Siemiatycki J. Impact de l'environnement et du milieu de travail sur le cancer : connaissances récentes. 9es Journées annuelles de santé publique (JASP), City of Québec, Quebec, November 2005.
132. Siemiatycki J. La recherche épidémiologique sur le cancer. Canadian Cancer Society - 2005 Annual Conference, City of Québec, Quebec, November 2005.
133. Siemiatycki J. Occupational EMF exposure and risk of cancer – methodological considerations. Workshop on the Future Needs of Electro-magnetic Fields Occupational Studies in the Electric Utility Industry, Edinburgh, September 2006.
134. Siemiatycki J. What is known about the modifiable causes of cancer and why we will not learn much more: Reflections on the decline of epidemiology as a tool to elucidate disease etiology. Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montréal, October 2006.
135. Siemiatycki J. Keynote Speaker. Environmental causes of cancer. 28th Annual Meeting of the International Association of Cancer Registries, Goiania, Brazil, November 2006.
136. Parent M.-E, Rousseau M.-C, Siemiatycki J, Boffetta P, Cohen A. Using the workplace as a window to study the role of diesel and gasoline engine emissions in lung cancer development. Invited abstract submitted to the Eleventh International Congress of Toxicology, Montréal, Quebec, July 2007.
137. Siemiatycki J. Keynote Speaker. The future of occupational epidemiology? 19th International Conference on Epidemiology in Occupational Health (EPICOH 2007), Banff, October 2007. *Occup. Environ. Med.* 2007 Dec; 64:46.

138. Siemiatycki J. Relationship between environmental risks and health of seniors. Workshop on Seniors' Health and the environment. Health Canada, Ottawa, February 2008.
139. Siemiatycki J. Freedom of research - is it threatening or threatened? Conference of Institutional Review Boards of Quebec, (4e Journées d'étude des CER), City of Québec, Quebec, October 2008.
140. Siemiatycki J. Cancer and Environment – Annual University of Montréal Medical Faculty Assembly, Montréal, December 2008.
141. Siemiatycki J. Impact de l'environnement et du milieu de travail sur les risques de cancer : méthodologie de recherche et résultats. Conférence en santé publique, Université Laval, May 2009.
142. Siemiatycki J. CIHR and Epidemiologic Research. CSEB, Ottawa, May 2009.
143. Siemiatycki J. Mode de vie, milieu de vie: les causes modifiables du cancer. (Lifestyles and environment: modifiable causes of cancer). Keynote address. Conference nationale pour vaincre le cancer, Montréal April 2010.
144. Siemiatycki J. Montréal case-control studies on occupation and cancer. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
145. Siemiatycki J. Modifiable causes of cancer and estimates of attributable fractions. Presentation for II International Course on occupational cancer, Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
146. Siemiatycki J. Asbestos and cancer in Quebec: a presentation of studies in three populations. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
147. Siemiatycki J. An overview of recognized environmental and lifestyle causes of cancer, and their contribution to the overall burden of cancer. International Congress of Pathophysiology, Montréal, September 2010.
148. Siemiatycki J. Les causes modifiables du cancer (Lifestyles and environment: modifiable causes of cancer). Conference annuelle de la Société du cancer du Canada, division Québec, November 2010.
149. Siemiatycki J. Alison McDonald's research on the impact of Medicare in Québec. Department of Epidemiology and Biostatistics, McGill University, Montréal, Quebec, May 2011.
150. Siemiatycki J. An overview of environmental causes of cancer. Special Symposium to honour Nobel Prize winner CRCHUM, Montréal, Quebec, June 2011.
151. Siemiatycki J. Review of IARC evaluation on cellphones and cancer. Congress of Epidemiology, Montréal, Quebec, June 2011.
152. Siemiatycki J. L'évidence concernant les risques de cancer liés à l'utilisation du téléphone cellulaire. Institut national de santé publique du Québec, October 2011.
153. Siemiatycki J. Do cellphones cause brain cancer? Canadian Cancer Research Conference, Toronto, November 2011.
154. Siemiatycki J. Do cellphones cause brain cancer? Canadian Center for Architecture. Public science lecture series, Montréal, Quebec, January 2012.
155. Siemiatycki J. Do cellphones cause brain cancer? McGill University Department of Epidemiology lecture series, Montréal, Quebec, March 2012.
156. Siemiatycki J. L'environnement et le risque de cancer. Table ronde. Conference annuelle de la Coalition Cancer, Montréal, Quebec, March 2012.
157. Siemiatycki J. An Overview of Modifiable Risk Factors for Cancer. CHUM Department of Medicine, Montréal, Quebec, March 2012.
158. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Grand Rounds, St-Mary's Hospital, Montréal, Quebec, September 2012.
159. Siemiatycki J. The epidemiology of cell phones and brain cancer. Centre hospitalier universitaire Vaudois, Lausanne, Suisse, October 2012
160. Siemiatycki J. Occupational causes of cancer. Annual meeting of Occupational & Environmental Medical Association of Canada, Montréal, Quebec, September 2013.
161. Siemiatycki J. Fraction of lung cancer that is legally attributable to smoking: a novel parameter. ISPED, Bordeaux, France, November 2013.

162. Siemiatycki J. Some challenges in environmental cancer research. Boston University School of Public Health, Boston, Massachusetts, February 2014.
163. Siemiatycki J. Les causes modifiables du cancer: le cancer peut être évité. Symposium de La Fondation Sauve Ta Peau, Montréal, Quebec, September 2014.
164. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. BIPS, Bremen, Germany, September 2015.
165. Siemiatycki J. Insights into the use of epidemiologic data in a class action lawsuit against the tobacco industry. CRCHUM division seminar, Montréal, Quebec, September 2015.
166. Siemiatycki J. Development of a methodology to estimate legally attributable fraction of lung cancer attributable to cigarette smoking. McGill Univ Dept of Epidemiology, Montréal, Quebec, October 2015.
167. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. SIRIC-BRIO Cancer Centre. Bordeaux, France, November 2015.
168. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Dept of Medicine, CHUM, Montréal, Québec, November 2015.
169. Siemiatycki J. Occupation and cancer. Conference for the 50th Anniversary of IARC, Lyon, June 2016.
170. Siemiatycki J. Contribution of epidemiology to knowledge on occupational risk factors for cancer. 34^e Congrès national de Médecine et Santé au Travail, Paris, France, June 2016.
171. Siemiatycki J. The influence of JC McDonald on the evolution of epidemiology in Canada. Symposium in honour of JC McDonald. McGill Univ., Montréal, Quebec, May 2017.
172. Siemiatycki J. A survey of knowledge on occupational causes of cancer. Keynote address. International Association of Cancer Registries, Utrecht, Netherlands, October 2017.
173. Siemiatycki J. La preuve statistique au tribunal : recours collectif en situation d'incertitude. Café-statistique de la Société des statisticiens français de la région parisienne, Paris, France, May 2018.

SCIENTIFIC PRESENTATIONS - OFFERED AND ACCEPTED

1. Siemiatycki J. Comparison of mail, telephone and home interview methods for health surveys. International Epidemiologic Association Meeting. Puerto Rico. August 1977.
2. Siemiatycki J, Day NE, Fabry J, Cooper, JA. Identification d'agents cancérigènes dans le milieu de travail: un nouveau système épidémiologique de monitoring. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
3. Siemiatycki J, Richardson L, Pless B. Equality in Medical Care under National Health Insurance in Montréal. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
4. Siemiatycki J. Discovering occupational carcinogens. International Symposium on Chemical Mutagenesis, Human Population Monitoring and Genetic Risk Assessment. Ottawa. October 1980.
5. Siemiatycki J, Richardson L, Gerin M. Discovering occupational carcinogens by a substance-based case-control approach-fieldwork considerations. International Epidemiologic Association Meeting. Edinburgh. August 1981.
6. Siemiatycki J, Colle E, West R, Belmonte M. Space-time clustering of juvenile-onset diabetes in Montréal. International Epidemiologic Association Meeting. Edinburgh. August 1981.
7. Siemiatycki J, Gerin M, Richardson L. Discovering occupational carcinogens by an exposure-based case-control approach: exposure assessment aspects. Second International Symposium on Epidemiology in Occupational Health. Montréal, August 1982.
8. Siemiatycki J, Gerin M, Lakhani R, Dewar R, Pellerin J, Richardson L. Nickel and cancer associations from a multicancer occupation exposure case-referent study. Symposium on Nickel in the Environment. Lyon, March 1983.
9. Gerin M, Siemiatycki J. La traduction des histoires professionnelles en histoires d'expositions chimiques: un défi pour l'hygiéniste du travail. Congrès de l'Association pour l'hygiène industrielle du Québec. Quebec, May 1983.
10. Siemiatycki J, Colle E, Campbell S, Belmonte M. Preliminary analysis of a case-control study of Type I diabetes mellitus. Baltimore, June 1985.

11. Siemiatycki J, Richardson L, Gerin M, Goldberg M, Dewar R. Associations between nine sites of cancer and nine organic dusts: results from a hypothesis-generating case-control study in Montréal. Society for Epidemiologic Research. Chapel Hill, North Carolina, June 1985.
12. Richardson L, Siemiatycki J, Gerin M, Goldberg M, Dewar R, Desy M, Campbell S, Wacholder S. Associations between several sites of cancer and nine organic dusts: results from a case-control study. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
13. Richardson L, Siemiatycki J. Case-control study methods: when to interview subjects and non-response bias. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
14. Soskolne C, Jhangri G, Checkoway, Risch H, Siemiatycki J, et al. Sulphuric acid exposure in laryngeal cancer: induction and latency estimates from a lagged exposure window analysis. XII Scientific Meeting of the International Epidemiology Assoc. Los Angeles, August, 1990.
15. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1989). Gastrointestinal illness and drinking water: a prospective epidemiological study. 57th Conjoint Meeting on Infectious Diseases (CACMID), Montréal, 25-29 November 1989, Résumé C-30.
16. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). Drinking water related gastrointestinal illnesses. 1990 Annual Meeting of the American Society for Microbiology, Anaheim California, 13-17 May 1990.
17. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). A prospective epidemiological study of drinking water related gastrointestinal illnesses. International Association on water Pollution Research and Control, Health Related Water Microbiology Group, Tubingen, West Germany, 1-6 April 1990.
18. Case BA, Dufresne A, Siemiatycki J, Fraser R. Decoding occupational history from total lung particulate analysis. II: A comparative study. Brit. Occ. Hyg. Soc.; Seventh International Symposium on Inhaled Particles, Edinburgh, September 1991, S4.5.
19. Suarez-Almazor M, Soskolne C, Fung K, Jhangri G, Burch D, Howe G, Miller A, Siemiatycki J, Lakhani R, Dewar R. Choice of summary worklife exposure measures in the estimation of risk: an empirical assessment. Canadian Epidemiology Symposium. Edmonton. May. 1991.
20. Siemiatycki J, Nadon L, Dewar R. Cancer risks due to occupational exposure to polycyclic aromatic hydrocarbons. 8th International Symposium on Epidemiology in Occupational Health, Paris, France, September 1991.
21. Bourbonnais R, Siemiatycki J. Socioeconomic variables and cancer risk. Canadian Society for Epidemiology and Biostatistics. Edmonton, May 1991.
22. Gerin M, Begin D, Siemiatycki J, Dewar R. Study on the validity of the NOES job-exposure matrix using industrial hygiene measurements obtained in Montréal. Conference on Retrospective Assessment of Occupational Exposure. IARC Lyon. April 1994.
23. *Camus M, Siemiatycki J. Estimating past asbestos fiber levels in the general population of asbestos mining towns in Quebec. International Society Environmental Epidemiology, Research Triangle Park, N.C. Sept. 1994.
24. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. Canadian Society for Epidemiology and Biostatistics. St-John's, Newfoundland, Aug 1995.
25. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. International Society for Environmental Epidemiology. Noordwijkerhout, Netherlands, Aug, 1995.
26. Case BW, Camus M, Siemiatycki J. Trends in Pathologic Diagnosis of Malignant Mesothelioma among Quebec Women 1970-1990. Royal College of Medicine. Montréal. Sept. 1995.
27. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational Risk Factors for Prostate Cancer. Canadian Society for Epidemiology and Biostatistics, St-John's, Newfoundland, Aug 1995.
28. *Camus M, Siemiatycki J. The Estimation of Past Asbestos Fiber Levels in Quebec Asbestos Mining Towns from 1900 to 1984. Canadian Society for Epidemiology & Biostatistics, St-John's, Newfoundland, Aug 1995.

29. *Camus M, Siemiatycki J, Dewar R. Non-Occupational Asbestos Exposure and Risk of lung Cancer in the Female Population of Asbestos-Mining Towns: Implications for Risk Assessments. Canadian Society for Epidemiology and Biostatistics Meeting, St-John's, Newfoundland, Aug 1995.
30. Payment P, Franco E, Siemiatycki J, Richardson L, Renaud G, Prevost M. Epidemiology studies of tap-water related gastrointestinal illnesses. Water Quality Technology Conference, New Orleans, Nov. 1995.
31. *Fritschi L, Siemiatycki J. Self-assessed versus expert-assessed occupational exposures. Canadian Society for Epidemiology and Biostatistics Meeting, St Johns, Newfoundland, Aug 1995.
32. Payment P, Siemiatycki J, Richardson L, Renaud G. Épidémiologie des maladies gastro-intestinales et respiratoires: incidence, fraction attribuable à l'eau et coûts pour la société. ACFAS, Montréal, May 1996.
33. *Fritschi L, Parent M-É, Siemiatycki J. Gastric cancer and occupation. Australasian Epidemiological Association, Victoria, Australia. July 1996.
34. *Camus M, Case BW, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.1: Environmental exposure assessment. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
35. Case BW, Camus M, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.2: Mesothelioma: observed vs. predicted. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
36. *Camus M, Siemiatycki J. Cancer risks due to non-occupational asbestos exposure. Can. Soc. for Epidemiol. & Biostat. London, Ontario, May 1997.
37. Weston TL, Aronson KJ, Howe GR, Nadon L, Siemiatycki J. Cancer mortality risk in a cohort of working men. Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
38. *Parent M-É, Siemiatycki J, Menzies L, Fritschi L, Colle E. Can Bacille-Calmette Guérin vaccination prevent insulin-dependent diabetes mellitus (IDDM)? Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
39. Wolf, S, Siemiatycki J, Beyersmann, D, Jockel, K. H. A case-control study of lung cancer - performance of a job-exposure matrix for cadmium, chromium, nickel, and stainless steel dust. Internat. Epidemiol. Assoc. European Region Meeting. Munster, Germany, Sept. 1997.
40. *Parent, M.E. Siemiatycki J. Exposition professionnelle aux émissions d'essence et de diesel, et cancer du poumon. ACFAS, Quebec, May 1998.
41. *Parent M-É, Siemiatycki J, Boffetta P. Occupational exposure to gasoline and diesel engine emissions and lung cancer. Soc. Epid. Res, Chicago, June 1998.
42. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Occupational exposure to gasoline and diesel exhausts and lung cancer. Inter. Soc. Environ. Epid, Boston, August 1998.
43. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Gasoline and diesel engine emissions in the workplace and lung cancer. PREMUS-ISEOH '98, Helsinki, Finland, Sept. 1998.
44. Leffondre K, Abrahamowicz M, Rachet B, Siemiatycki J. Modeling smoking history: A comparison of different approaches. Congress of Epidemiology, Toronto, June 2001.
45. Fritschi L, Nadon L, Benke G, Lakhani R, Latreille B, Parent M-É, Siemiatycki J. Validation of expert assessment of occupational exposures X2001 – Occupational Exposure Assessment for Epidemiology and Practice, Gothenburg, Sweden, June 2001.
46. Parent M-É, Siemiatycki J, Desy M. Case-control study of occupational exposures and risk of prostate cancer among farmers. Case-control study of occupational exposures and risk of prostate cancer among farmers, Toronto, June 2001.
47. Siemiatycki J, Camus M, Parent M-É, Richardson L, Desy M, Case BW. Case-control study of pleural mesothelioma among women in Quebec chrysotile mining regions. Inhaled Particles IX (BOHS), Cambridge, United Kingdom, September 2001.
48. Jockel K-H, Wolf S, Ahrens W, Jahn I, Pohlabein H, Beyersmann D, Siemiatycki J. Cadmium as a human lung carcinogen. Jahrestagung der Deutschen Arbeitsgemeinschaft für Epidemiologie (DAE) [Annual convention of the German epidemiology working group], Garmisch-Partenkirchen, Germany, September 2001.

49. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Annual Meeting of the Statistical Society of Canada (SSC). Hamilton, Ontario. May 2002.
50. Parent M-É, Siemiatycki J, Desy M. Association between Alcohol Consumption and Each of 23 Types of Cancer in Men. Soc. Epid. Res, Palm Desert, California, June 2002.
51. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Society for Epidemiologic Research (SER), Palm Desert, California, June 2002.
52. Rachet B, Parent M-É, Siemiatycki J. Welding Fumes and Lung Cancer: A Case-Control Study, Soc. Epidemiol. Res, Palm Desert, California, June 2002.
53. Rachet B, Abrahamowicz M, Sasco A, Siemiatycki J. Flexible estimation of the distribution of lag in the effects of exposures and interventions. 34th Annual SER Meeting. Palm Desert, California. June 2002.
54. Abrahamowicz M, Mackenzie T, Leffondre K, Du Berger R, Siemiatycki J. Joint modeling of time-dependent and non-linear effects of continuous predictors in survival analysis, with application to reassess the impact of intensity of past smoking on the risks of lung cancer in ex-smokers. 17th International Workshop on Statistical Modeling, Chania, Greece, July 2002.
55. Parent M-É, Siemiatycki J, Desy M. Exposure to chemical agents during leisure activities and risk of non-Hodgkin's lymphoma. Inter. Epidemiology Association, Montréal, August 2002.
56. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. International Epidemiological Association (IEA), World Congress of Epidemiology, Montréal, Québec, August 2002.
57. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Exposure-response relationships between cigarette smoking and male lung cancer from a case-control study in Montréal: generalized additive model approach. International Epidemiology Association (IEA) XVI World Congress of Epidemiology. Montréal, Québec. August 2002.
58. Parent M-É, Rousseau M-C, Siemiatycki J, Desy M. Body mass index and male cancer incidence at twelve different sites. Body mass index and male cancer incidence at twelve different sites. Halifax, Nova Scotia, June 2003.
59. Desautels N, Siemiatycki J, Parent M.E. Association between lifetime consumption of coffee, tea, and soft drinks, and incidence of eleven types of cancer: a case-control study. CSEB 2003 Biennial Meeting. Halifax, Nova Scotia, June 2003.
60. Parent M-É, Siemiatycki J, Desy M. Association between beta-carotene intake and risk of cancer at several sites. Society for Epidemiologic Research, Atlanta, Georgia, June 2003.
61. Parent M-É, Siemiatycki J, Laplante O, Desy M. Risk of lung cancer and mesothelioma associated with occupational exposure to Asbestos: A population-based case-control study in Montréal, Canada. International Society for Environmental Epidemiology, Perth, Australia, September 2003.
62. Parent M-É, Siemiatycki J, Laplante O, Désy M. Occupational exposure to asbestos and risk of lung cancer and mesothelioma: results from a population-based-case-control study in Montréal. CARWH Conference. Montréal, Québec, October 2003.
63. Parent M-É, Siemiatycki J, Latreille B, Désy M. Lifetime Occupational Physical Activity and Prostate Cancer Risk. Society for Epidemiologic Research. Salt Lake City, Utah, June 2004.
64. Parent M-É, Rousseau M.C, Siemiatycki J, Boffetta P, Cohen A. Contrasting evidence when using hospital or population controls: the example of the association between exposure to gasoline and diesel exhaust, and lung cancer. 16th conference of the International Society for Environmental Epidemiology (ISEE). New York City, August 2004.
65. De Guire L, Lebel G, Gingras S, Levesque B, Camus M, Provencher S, Case B, Langlois A, Laplante O, Siemiatycki J, Lajoie P. Epidemiology of Asbestos-related diseases in Québec, Canada. EPICOH 2004. Melbourne, Australia, October 2004.
66. Richardson H, Aronson K, Parent M-É, Siemiatycki J. Risk of cancer due to occupational exposure to six types of chlorinated hydrocarbons. EPICOH, Melbourne, Australia, October 2004.

67. De Guire L, Lebel G, Gingras S, Levesque B, Camus M, Provencher S, Case B, Langlois A, Laplante O, Siemiatycki J, Lajoie P. Épidémiologie des maladies reliées à l'exposition à l'amiante au Québec. Board Meeting, Canadian Association of University Teachers. Ottawa, November 2004.
68. Rousseau M-C, Parent M-É, Siemiatycki J. Occupational exposure to lead and risk of cancer in a population-based case-control study from Montréal, Canada. Canadian Association for Research on Work and Health, Vancouver, May 2005.
69. Parent M-É, Rousseau M-C, Siemiatycki J, Desy, M. Using proxy respondents when assessing occupational circumstances in a case-control study of cancer: For better or for worse? Canadian Association for Research on Work and Health, Vancouver, May 2005.
70. *Momoli F, Siemiatycki J, Parent M-É, Abrahamowicz M. Semi-Bayes modeling in a study of lung cancer and multiple occupational chemicals: Comparison of results for five suspected lung carcinogens. Canadian Association for Research on Work and Health, Vancouver, May 2005.
71. *Momoli F, Siemiatycki J, Parent M-É, Abrahamowicz M. Semi-Bayes models: An empirical comparison of modeling approaches in a study of lung cancer and occupational chemicals. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
72. Rousseau M-C, Camus M, Case B, Siemiatycki J. Incidence of pleural mesothelioma among women in Québec, 1970-1989: A comparison between asbestos mining and non-mining areas. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
73. Leffondre K, Abrahamowicz M, Siemiatycki J. Modeling smoking history using an overall indicator of exposure. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
74. Parent M-É, Siemiatycki J, Latreille B, Desy M. Is occupational physical activity associated with cancer risk among men? Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
75. *Ramanakumar AV, Parent M-É, Menzies R, Camus M, Siemiatycki J. Previous history of lung disease and risk of lung cancer in Montréal. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
76. *Benedetti A, Parent M-É, Siemiatycki J. Alcohol consumption and lung cancer risk in two case-control studies in Montréal, Canada. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
77. Leffondre K, Abrahamowicz M, Siemiatycki J. Modeling smoking history using an overall indicator of exposure. 26th Annual Conference of the International Society for Clinical Biostatistics (ISCB), Szeged, Hungary, August 2005.
78. Rousseau M.-C, Parent M-É, Siemiatycki J. Exposition professionnelle au plomb et risque de cancer : Étude de cas-témoin basée sur la population de Montréal, Qc. Environnement et santé : Congrès international de l'Association des épidémiologistes de langue française (ADELF), Québec, September 2005.
79. *Ramanakumar AV, Parent M-É, Siemiatycki J. Residential fuel exposures and risk factors for lung cancer: Evidence from two population-based case-control studies in Montréal. Spring Colloquium: Environmental Health Research Network (RRSE), Montréal, May 2006.
80. Sharek M, Rousseau M-C, Siemiatycki J, Parent M-É. Antioxydants et prévention du cancer du poumon : où en sommes-nous? Spring Colloquium: Environmental Health Research Network (RRSE), Montréal, May 2006.
81. Parent M-É, Shareck M, Désy M, Rousseau M-C, Siemiatycki J. Night Work and Risk of Prostate and Colon Cancers. Second North American Congress of Epidemiology, Seattle, June 2006.
82. Rousseau M-C, Parent M-É, Siemiatycki J. Exposure to lead compounds, occupation, and risk of cancer. Second North American Congress of Epidemiology, Seattle, June 2006.
83. *Ramanakumar AV, Parent M-É, Siemiatycki J. Risk of lung cancer from traditional heating and cooking fuels in Montréal. 2006 American Association for Cancer Research (AACR) International Conference on Frontiers in Cancer Prevention Research, Boston, November 2006.

84. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-E. Antioxydants et prévention du cancer du poumon: où en sommes-nous? Second Conference of the Association des étudiantes et étudiants en Santé Publique de l'Université de Montréal, Montréal, February 2007.
85. *Liu A, Abrahamowicz M, Siemiatycki J. Selected Methodological Issues in Testing and Estimating Sex Interactions with Multi-dimensional Exposures: a Simulation Study. 3rd Annual GENESIS (Gender and Sex Determinants of Cardio-vascular Disease: From Bench to Beyond) Montréal Meeting, Montréal, March 8-9, 2007.
86. *Ramanakumar AV, Parent M-É, Siemiatycki J. Exposure to painting-related occupations and risk of lung cancer: results from two case-control studies in Montréal. Oral presentation, Canadian Society for Epidemiology and Biostatistics, Calgary, May 2007.
87. Parent M-É, Rousseau M-C, Pintos J, Nicolau B, Désy M, Siemiatycki J. Are men reporting a history of anxiety, depression or insomnia at increased risk of cancer? Annual Meeting of the Canadian Society for Epidemiology and Biostatistics, Calgary, May 2007.
88. *Pintos J, Parent M-É, Rousseau M-C, Siemiatycki J. Risk of mesothelioma associated with occupational exposure to asbestos: Evidence from two case-control studies in Montréal, Canada. Annual Meeting of the Canadian Society for Epidemiology and Biostatistics, Calgary, May 2007.
89. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Dietary antioxidants intake and risk of lung cancer: A population-based case-control study. Poster presentation, 2007 CSEB Student Conference, Calgary, Alberta, May 2007.
90. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Dietary antioxidants intake and risk of lung cancer: a population-based case-control study. Poster presentation, Spring 2007 Conference of the Environmental Health Research Network (RRSE-FRSQ), Montréal, May, 2007.
91. Parent M-É, Rousseau M-C, Pintos J, Nicolau B, Désy M, Siemiatycki J. Is there a link between stress at work and cancer risk? Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007;165(11)Suppl:S3.
92. Nicolau B, Parent M-É, Rousseau M-C, Désy M Siemiatycki J. Childhood socioeconomic position in relation to cancer: evidence from a Canadian population based case-control study. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007;165(11)Suppl:S77.
93. *Pintos J, Parent M-É, Rousseau M-C, Siemiatycki J. Occupational Exposure to Asbestos and Man-Made Vitreous Fibers, and Risk of Lung Cancer: evidence from two case-control studies in Montréal, Canada. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007; 165(11) Suppl: S102.
94. Rousseau M-C, Parent M-É, Desy M, Siemiatycki J. History of allergic disease and risk of cancer. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007;165(11)Suppl:S100.
95. *Momoli F, Parent M-É, Abrahamowicz M, Nadon L, Lakhani, Latreille B, Krewski D, Siemiatycki J. Lung cancer risk from selected occupational chemicals. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007; 165(11)Suppl:S102.
96. *Momoli F, Parent M-É, Abrahamowicz M, Nadon L, Lakhani, Latreille B, Krewski D, Siemiatycki J. Lung cancer risk from selected occupational chemicals. Annual Meeting of the Society for Epidemiologic Research, Boston, June 2007. American Journal of Epidemiology 2007; 165(11) Suppl: S102.
97. *Liu A, Abrahamowicz M, Siemiatycki J. Testing and estimating interactions with multi-dimensional exposures: A simulation study. 28th Annual Conference of the International Society for Clinical Biostatistics, Alexandroupolis, Greece, July-August 2007.
98. Parent M-E, Rousseau M-C, Siemiatycki J, Goldberg M, Aprikian F, Saad F, Karakiewicz P. Main determinants of response rates in a large population-based case-control study of environmental, lifestyle and genetic factors, and prostate cancer in Montréal, Canada. Making Connections: A Canadian Cancer Research Conference, Toronto, November 15-17, 2007.
99. *Liu A, Abrahamowicz M, Siemiatycki J. Testing and estimating interactions with multi-dimensional exposures: A simulation study. 10e Congrès annuel des étudiants, stagiaires et résidents du centre de recherche du CHUM. Montréal, December 18, 2007.

100. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Fruit and vegetables, and risk of lung cancer, by smoking intensity. Society for Epidemiologic Research, Chicago, June 2008.
101. Parent M-É, Siemiatycki J, Goldberg M, Désy M. Birth weight, obesity during childhood, adolescence and adulthood, and prostate cancer - Preliminary data from the PROTEuS study. Society for Epidemiologic Research, Chicago, June 2008. American Journal of Epidemiology 2008 ; 167 (Suppl.): S62
102. Leffondré K, Wynant W, Cao Z, Siemiatycki J. A comprehensive smoking index to model smoking history in cancer studies. Society for Epidemiologic Research, Chicago, June 2008.
103. *Beveridge R, Pintos J, Parent M-É, Asselin J, Siemiatycki J. Risk of lung cancer after occupational exposure to cadmium, chromium VI, and nickel. Society for Epidemiologic Research, Chicago, June 2008.
104. *Liu A, Abrahamowicz M, Siemiatycki J. Methodological challenges in testing and estimating interactions with multi-dimensional exposures. Society for Epidemiologic Research, Chicago, June 2008.
105. Leffondré K, Wynant W, Cao Z, Abrahamowicz M, Siemiatycki J. A weighted Cox model for case-control data with time-dependent exposures. 29th Annual Conference of the International Society for Clinical Biostatistics, Copenhagen, August 17-21, 2008.
106. Koushik A, Parent M-É, Siemiatycki J. Characteristics of menstruation and pregnancy and the risk of lung cancer in women. 6th Annual American Association for Cancer Research, Frontiers in Cancer Prevention Research Meeting, Philadelphia, November 16-19 - 2008
107. Olsson A.C., Gustavsson P, Kromhout H, Siemiatycki J, et al. Pooled Analyses on Diesel Motor Exhaust and Lung Cancer in Europe and Canada. Poster presentation. 29th ICOH International Congress on Occupational Health, Cape Town, South Africa, March 2009.
108. Shareck M, Rousseau M-C, Siemiatycki J, Parent M-É. Dietary Intake of Antioxidants and Risk of Four Histological Subtypes of Lung Cancer: a Population Based Case-Control Study. Oral presentation at the Canadian Society for Epidemiology and Biostatistics (CSEB) and Association of Public Health Epidemiologists in Ontario (APHEO) Joint Conference, Ottawa, Ont. May 2009
109. Nkosi MT, Rousseau M-C, Parent M-É, Siemiatycki J. Comparison of indicators of financial situation in the context of an epidemiological study. Poster presentation at the Canadian Society for Epidemiology and Biostatistics (CSEB) and Association of Public Health Epidemiologists in Ontario (APHEO) Joint Conference, Ottawa Ont, May 2009.
110. Nkosi MT, Rousseau M-C, Parent M-É, Siemiatycki J. Studying socio-economic status and lung cancer risk; How important Is the modelling of smoking? Poster presentation at the Canadian Society for Epidemiology and Biostatistics (CSEB) Student Conference, Ottawa Ont, May 2009.
111. Rousseau M-C Parent M-E, Nicolau B, Koushik A, Siemiatycki J. Body mass index and lung cancer risk in a population-based case-control study from Montréal, Canada. Poster presentation at the 42nd Annual Meeting of the Society for Epidemiological Research (SER) Meeting Anaheim Ca, June 23-26 2009.
112. *Pintos J, Parent M-E, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer; evidence from case-control study in Montréal. Oral presentation. 42nd Annual Meeting of the Society for Epidemiologic Research Meeting (SER), Anaheim, June 23-26 2009.
113. *Perron S, Jacques L, Siemiatycki J, Ducharme F. Home multifaceted environmental interventions to improve asthma control: A systematic review. 137th Annual Meeting of the American Public Health Association (APHA), November 7-11 2009, Philadelphia, PA.
114. *Wynant W, Siemiatycki J, Parent M-E, Rousseau M-C. Exposition professionnelle au plomb et risque de cancer du poumon. Présentation orale, Congrès Armand Frappier, Bromont (Qc), Novembre 2009.
115. Kâ K, El-Zein M, Parent M-É, Siemiatycki J, St-Pierre Y, Rousseau M-C. Antécédent médical d'asthme ou d'eczéma et risque de cancer: une étude cas-témoins à base populationnelle. Présentation orale, Congrès Armand Frappier, Bromont (Qc), Novembre 2009.
116. Soskolne CL, Jhangri GS, Scott HM, Brenner DR, Siemiatycki J, Lakhani RA, Gérin M, Dewar R, Miller AB, Risch H. A population based case-control study of occupational exposure to acids and the risk of lung cancer: evidence for specificity with laryngeal cancer. Poster presentation at INSIGHTS'09, School of Public Health, University of Alberta, Edmonton, Alberta, November 12 2009.

117. *Pintos J, Lavoué L, Van Tongeren M, Kauppinen T, Richardson L, Sleguwenhoek A, Lakhani R, Cardis E, Siemiatycki J. Comparison of exposure estimates in FINJEM with expert-based assessments performed in Montréal. Part I: Exposure prevalence. Oral presentation. Epidemiology in Occupational Health (EPICOH), Taipei, April 2010.
118. Lavoué J, Pintos J, Van Tongeren M, Kauppinen T, Richardson L, Sleguwenhoek A, Lakhani R, Cardis E, Siemiatycki J. Comparison of exposure estimates in FINJEM with expert-based assessments performed in Montréal. Part II: Exposure levels. Oral presentation. Epidemiology in Occupational Health (EPICOH), Taipei, April 2010.
119. *Christensen KY, Naidu A, Parent M-E, Pintos J, Siemiatycki J, Koushik A. The risk of lung cancer related to dietary intake of flavonoids. Annual Meeting of the Society for Epidemiologic Research (SER), Seattle, Washington, June 2010.
120. *Wynant W, Siemiatycki J, Parent M-E, Rousseau M-C. Occupational exposure to lead compounds and lung cancer. SER, Seattle, June 2010.
121. *Liu A, Abrahamowicz M, Siemiatycki J. Methodological challenges in testing and estimating interactions with multi-dimensional exposures. Annual Meeting of the Society for Epidemiologic Research (SER), Seattle, June 2010.
122. Rousseau M-C, Conus F, Parent M-É, Siemiatycki J. History of allergic diseases and risk of lung cancer. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
123. Leffondré K, Wynant W, Cao Z, Siemiatycki J. A comprehensive smoking index to model smoking history in cancer studies. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
124. *Liu A, Abrahamowicz M, Siemiatycki J. When Interaction Estimates in Logistic Regression are Confounded? Oral presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
125. *Vallièrès É, Siemiatycki J, Lavoué J, Pintos J, Parent M-E. Risk of lung cancer after exposure to welding fumes in two population-based case-control studies. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
126. *Mahboubi A, Koushik A, Siemiatycki J, Lavoué J, Rousseau M-C. Occupational exposure to formaldehyde and risk of lung cancer. Poster presentation Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):762-S.
127. *Mahboubi A, Abrahamowicz M, Siemiatycki J. Simulation study of multiple logistic regression estimates for multiple correlated exposures measured with errors. Poster presentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
128. *Al-Zoughool M, Pintos J, Richardson L, Parent M-É, Ghadirian P, Krewski D, Siemiatycki J. Exposure to environmental tobacco smoke and risk of lung cancer: evidence from a case-control study in Montréal, Canada. Poster presentation. Third North American Congress of Epidemiology, Montréal, Quebec, Canada, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
129. El-Zein M, Parent M-É, Nicolau B, Koushik A, Siemiatycki J, Rousseau M-C. Smoking, body mass index and lung cancer risk. Poster presentation. Third North American Congress of Epidemiology, Montréal, Quebec, Canada, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
130. Karp I, Abrahamowicz M, Leffondré K, Siemiatycki J. Development of a method for assessment of risk of lung cancer. Poster presentation. Third North American Congress of Epidemiology, Montréal, Quebec, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
131. Momoli F, Parent M-E, Siemiatycki J, Platt R, Richardson L, et al. A probabilistic multiple-bias model applied to a study of mobile phone use and risk of glioma. Third North American Congress of Epidemiology, Montréal, Quebec, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
132. Siemiatycki J, Richardson L, Kincl L, Schlaefel K, Cardis E. Oral presentation. INTEROCC Study: Social Class and The Risk of Glioma Brain Tumours. International Society for Environmental Epidemiology (ISEE), Barcelona, Spain, September 2011.

133. Siemiatycki J, Richardson L, Kincel L, Schlaefter K, Cardis E. Oral presentation. INTEROCC Study: Social Class and The Risk of Meningioma Brain Tumours. International Society for Environmental Epidemiology (ISEE), Barcelona, Spain, September 2011.
134. Kendzia B, Pesch B, Jöckel K.-H, Kromhout H, Straif K, Brüning T, on behalf of the SYNERGY Working Group. Lung cancer risks of welding in a pooled analysis of case-control studies. Oral presentation. 7th International Conference on Science of Exposure Assessment (X2012), Edinburg, Scotland, July 2012.
135. Olsson A.C, Vlaanderen J, Vermeulen R, Kromhout H, Pesch B, Straif Kurt on behalf of the SYNERGY study Group. Improved risk estimation through advanced exposure modelling in community-based studies: the example of occupational asbestos exposure in the SYNERGY project. Oral presentation. 7th International Conference on Science of Exposure Assessment (X2012), Edinburgh, Scotland, July 2012.
136. *Lacourt A, Lavoué J, Labrèche F, Siemiatycki J. Gender differences in occupational exposures assessed by experts in a community based-case control study of lung cancer. Oral presentation 7th International Conference on the Science of Exposure (X2012), Edinburgh, Scotland, July 2012.
137. *Pasquet R, Karp I, Siemiatycki J, Koushik A. Intake of black tea and coffee and the risk of lung cancer. E-poster. UICC World Cancer Congress, Montréal, Quebec, 27-30 August 2012.
138. *Vallièrès E, Siemiatycki J, Lavoué J, Pintos J, Parent M-E. Risk of three histological types of lung cancer after exposure to welding fumes. Poster presentation, UICC World Cancer Congress, Montréal, Quebec, 27-30 August 2012.
139. *Rivera M, *Vizcaya D, Pintos J, Abrahamowics M, Siemiatycki J. Association between exposure to engine emissions and lung cancer. 23rd International Conference on Epidemiology in Occupational Health (EPICOH), Utrecht, Netherlands, 18-21 June 2013.
140. *Vizcaya D, Lavoué J, Bégin D, Pintos J., Richardson L, *Rivera M, Siemiatycki J. Risk of eight types of cancer and cleaning-related exposures in a case-control study. 23rd International Conference on Epidemiology in Occupational Health (EPICOH), Utrecht, Netherlands, 18-21 June 2013.
141. *Vizcaya D, Lavoué J, Pintos J, Richardson L, Siemiatycki J. Lung cancer and cleaning-related exposures: results from two case-control studies. 23rd International Conference on Epidemiology in Occupational Health (EPICOH), Utrecht, Netherlands, 18-21 June 2013.
142. Turner M-C, Benke G, Bowman J, et al. Occupational exposure to extremely low frequency magnetic fields and brain tumour risks in the INTEROCC study. Environment and Health – Joint meeting of the International Society for Environmental Epidemiology (ISEE), the International Society for Exposure Sciences (ISES) and the International Society for Indoor Air Quality (ISIAQ), Basel, Switzerland, 19-23 August 2013.
143. Lavoué J, Labrèche F, Richardson L, Goldberg M, Parent M-E, Siemiatycki J. CANJEM: a general population job exposure matrix based on past expert assessments of exposure to over 250 agents. 24th International Conference on Epidemiology in Occupational Health (EPICOH), Chicago, Illinois, 24-27 June 2014. [abstract] Occupational & Environmental Medicine. 2014;71 (Suppl 1):A48.
144. *Ho V, Parent M-E, Pintos J, Abrahamowicz M, Gauvin L. Siemiatycki J, Koushik A. Lifetime occupational physical activity and lung cancer risk. 17^{ème} Congrès des étudiants, stagiaires et résidents du CRCHUM, Montréal, Quebec, December 2014.
145. Turner M C, Sadetzki S, Eastman Langer C, Figuerola J, Armstrong BK, Chetrit A, Giles GG, Krewski D, Hours M, McBride /ML, Parent M-E, Richardson L, Siemiatycki J, Woodward A, Cardis E. Impact of case:control matching strategies on associations between cellular telephone use and glioma risk in the INTERPHONE study. International Society for Environmental Epidemiology (ISEE), Seattle, Washington, 25 August 2014.
146. *Dutczak H, Siemiatycki J, Koushik A. Exposure to stressful life events and lung cancer risk. 10^{ème} Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Quebec, February 2015.
147. *Xu M, Richardson L, Campbell S, Siemiatycki J. Trends and Characteristics of Response Rates in Case-Control Studies of Cancer. 10^{ème} Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Montréal, Quebec, February 2015.

148. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. L'association entre l'exposition occupationnelle aux métaux et le cancer du cerveau. 10ème Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Montréal, Quebec, February 2015.
149. *Dutczak H, Siemiatycki J, Koushik A. Stressful life events and lung cancer risk. Canadian Society for Epidemiology and Biosatistics (CSEB), Mississauga, Ontario, 1-4 June 2015.
150. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. The association between occupational exposure to metals and metalloids and brain cancer risk. Canadian Society for Epidemiology and Biosatistics (CSEB), Mississauga, Ontario, 1-4 June 2015.
151. *Xu M, Richardson L, Campbell S, Siemiatycki J. Trends and Characteristics of Response Rates in Case-Control Studies of Cancer. Canadian Society for Epidemiology and Biosatistics (CSEB), Mississauga, Ontario, 1-4 June 2015.
152. Behrens T, Groß I, Siemiatycki J, Conway D, Jöckel K-H, Olsson A, Kromhout H, Straif K, Schüz J, Hovanec J, Kendzia B, Pesch B, Brüning T. Niedriges berufliches Prestige, soziale Mobilität und Lungenkrebs – die SYNERGY-Studie. German Epidemiology Association (DGEpi), Potsdam, Germany, September 2015.
153. *Carrier M, Kestens Y, Siemiatycki J. Nuisances environnementales et risques pour la santé. AQTR, Montréal, Quebec, 15 September 2015.
154. *Sauvé JF, Siemiatycki J, Labrèche F, Lavoué J. Development of the CANJEM job exposure matrix: Bayesian modelling of occupational exposures assigned by experts to over 30000 jobs spanning 1920-2005. The International Society of Exposure Science (ISES), Henderson, Nevada, 18-22 October 2015.
155. Vila J, Bowman JD, Richardson L, Kincl L, Conover D, van Tongeren M, Mann S, Vecchia P, McLean D, Cardis E, on behalf of the INTEROCC Study Group. Assessing cumulative exposures to electromagnetic fields: From source-based measurements to individual lifetime exposure estimates. The International Society of Exposure Science (ISES) Henderson, Nevada, 18-22 October 2015.
156. *Karumanchi S, Hatsopoulou M, Richardson L, Siemiatycki J. Methodology for exposure assessment for UFPs in the Grand Montréal Region. Oral presentation. 11th Annual Symposium of the Student Association in Public Health at the Université de Montréal (AÉÉSPUM), Montréal, Quebec, 9 February 2016.
157. *Carrier M, Apparicio P, Kestens Y, Séguin AM, Pham H, Crouse D, Siemiatycki J. Application of a global environmental equity index in Montréal: diagnostic and further implications, AAG, San Francisco, California, 30 March 2016.
158. *Carrier M, Apparicio P, Kestens Y, Séguin A-M, Pham H, Crouse D, Siemiatycki J. Application d'un indice d'équité environnementale à Montréal: établissement d'un diagnostic pour cibler les secteurs et les groupes les plus vulnérables, ACFAS, Montréal, Quebec, 11 May 2016.
159. *Carrier M, Kestens Y, Crouse D, Siemiatycki J. Lung cancer and exposure to Nitrogen Dioxide and Traffic in Montréal, World Conference on Transport Research, Shanghai, China, 10 July 2016.
160. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Patterns and trends in quality of response rate reporting in case-control studies of cancer. 18th Congress of Students, Interns and Residents of CRCHUM, Montréal, Quebec, 4 May 2016.
161. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Time trends and study design determinants of response rates in case-control studies of cancer. 18th Congress of Students, Interns and Residents of CRCHUM, Montréal, Quebec, 4 May 2016.
162. *Karumanchi S, Hatsopoulou M, Richardson L, Thierry B, Goldberg M, Siemiatycki J. Land use regression model of UFPs in the Grand Montréal Region. Oral presentation. Canadian Society for Epidemiology and Biostatistics, Winnipeg, Manitoba, 8-10 June 2016.
163. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Subject response rates in case-control studies of cancer: quality of reporting, time trends, and study design determinants. Epidemiology Congress of the Americas, Miami, Florida, 21-24 June 2016.
164. *Rémen T, Siemiatycki J, Lavoué J. Impact of inter-coder differences in occupation and industry classification coding on exposure estimates obtained via job-exposure matrix: example of gasoline engine

- emissions in CANJEM. Oral presentation. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
165. *Sauvé JF, Lavoué J, Siemiatycki J, Parent ME. Evaluation of a hybrid expert approach for retrospective assessment of occupational exposures in a population-based study of prostate cancer in Montréal, Canada. Oral presentation. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
 166. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. The association between occupational exposure to metals and metalloids and brain cancer risk. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
 167. Russ D, Rémen T, Ho KY, Chow WH, Davis F, Hofmann J, Huang H, Purdue M, Schwartz K, Siemiatycki J, Zhang Y, Silverman D, Johnson C, Lavoué J, Friesen M. Recommendations for prioritizing expert review of free-text job descriptions that underwent computer-based coding using the SOCcer algorithm. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
 168. *Sauvé JF, Labrèche F, Richardson L, Goldberg MS, Parent MÉ, Siemiatycki J, Lavoué J. Development of the CANJEM Canadian general-population job-exposure matrix from past expert evaluations. Oral presentation. Canadian Association for Research on Work and Health (CARWH) conference, Toronto, Ontario, October 2016.
 169. *Rémen T, Siemiatycki J, Lavoué J, Verner MA. Impact of inter-coder differences in occupation and industry classification coding on exposure estimates obtained via job-exposure matrix: example of gasoline engine emissions in CANJEM. Poster. International Society of Exposure Science (ISES) 2016 Annual Meeting, Utrecht, Netherlands, 9-13 October 2016.
 170. Grundy A, Ho V, Parent ME, Siemiatycki J, Koushik A. Lifetime recreational moderate-to vigorous physical activity and the risk of ovarian cancer by subtype. Poster presentation. 2016 American Institute for Cancer Research (AICR) Research Conference, North Bethesda, Maryland, 14-16 November 2016.
 171. Grundy A, Ho V, Parent ME, Siemiatycki J, Koushik A. The impact of menopausal status on the association between moderate-to-vigorous physical activity among participants in the Prevention of OVArian Cancer in Quebec (PROVAQ) study. Oral Presentation. Canadian Society for Epidemiology and Biostatistics 2017 Biennial Conference, Banff, Alberta, 1 June 2017
 172. Bowman JD, Vila J, Richardson L, Kincl L, Cardis E on behalf of the INTEROCC Study Group. Occupational Exposures to Radio-frequency Electric Fields Assessed for the INTEROCC Study of Brain Cancer. Oral presentation. American Industrial Hygiene Association conference, Seattle, Washington, 4-7 June 2017.
 173. *Karumanchi S, Siemiatycki J, Hatzopoulou M. Some challenges in measuring ultra-fine particles and developing a land use regression model. Oral presentation. Canadian Society for Epidemiology and Biostatistics (CSEB) 2017 Biennial Conference, Banff, Alberta, 30 May 2017.
 174. *Sauvé JF, Davies HW, Parent MÉ, Peters CE, Siemiatycki J, Sylvestre MP, Lavoué J. Development of quantitative estimates of wood dust exposure in a Canadian general population job-exposure matrix based on past expert assessments. 26th Conference on Epidemiology in Occupational Health (EPICOH 2017), Edinburgh, Scotland, August 2017.
 175. Ho V, Xu M, Pintos J, Lavoué J, Abrahamowicz M, Rousseau M.C, Richardson L, Siemiatycki J. Occupational exposures to leaded and unleaded gasoline engine emissions and lung cancer risk. Canadian Cancer Research Conference, Vancouver, British Columbia, 5-7 November 2017.
 176. Lequy E, Siemiatycki J, Leblond S, et al. Moss biomonitoring as an alternative to assess exposure to atmospheric metals in environmental epidemiology: the example of the bramm network and the gazel cohort. Poster. SEE Young 2018, Early Career Researchers Conference on Environmental Epidemiology – Together for a Healthy Environment, Freising, Germany, 19–20 March 2018. Occup Environ Med 2018;75:A27.
 177. Ho V, Parent MÉ, Lavoué J, Zhu Y, Siemiatycki J, Koushik A. Gender Differences in Occupational Physical Activity. Oral presentation. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario. 26-30 August 2018.

178. *Xu M, Ho V, Siemiatycki J. Association between occupational exposure to textile fibre dusts and lung cancer in a population-based case-control study in Montréal: a preliminary analysis comparing results from three analytical methods. Oral presentation. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
179. Zhu Y, Lavoué J, Parent MÉ, Siemiatycki J, Koushik A, Ho V. Occupational Physical Activity and Lung Cancer Risk among Participants of the Alberta's Tomorrow Project. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
180. *Karumanchi S, Siemiatycki J, Richardson L, Hatzopoulou M. Estimating exposure to Ultrafine Particles in the Greater Montreal Area among case-control study subjects: Comparison of classical land use regression model with a model based on Bayesian principles - Proposal. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
181. van Tongeren M, Dirkx E, Lavoué J, Siemiatycki J, Ho V. Assessment of Occupational Exposure to Endocrine Disrupting Agents. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.

* First author was under supervision of J. Siemiatycki when this work was carried out

GRANTS AND CONTRACTS RECEIVED

1. Comparison of three methods for conducting household health surveys; Nat. Health Res & Devel. Prog. (NHRDP); \$27,000; 1974-76.
2. Pilot study of a case-control monitoring system for discovering occupational carcinogens; Conseil de la recherche en santé (CRSQ); \$80,000; 1978-1980.
3. Établissement du jeune chercheur; CRSQ; \$15,000; 1979-80.
4. Analyse de santé auprès de 1600 ménages montréalais; Ministère des affaires sociales (MAS); \$12,708; 1980
5. Dépistage des facteurs cancérigènes de l'environnement professionnel montréalais: étude pilote; Commission des accidents du travail; \$59,093 ; 1980-82.
6. Registry of patients with Juvenile Onset Diabetes in Québec; NHRDP; \$35,478*; 1980-85; (P.I. Dr E. Colle).
7. Secondary analysis of a health survey in Montréal: methodologic issues and comparison of morbidity and health care utilization between social groups; NHRDP-H&W Can.; \$15,000; 1981-82.
8. Exposure-based case-control approach to discovering occupational carcinogens; NHRDP-H&W Can.; \$129,258; 1981-83.
9. An exposure-based case-control approach to discovering occupational carcinogens; NCIC; \$131,842; 1981-83.
10. Variation in sex ratios of cancer between geographic areas; NCIC; \$3,227; 1982-84.
11. Équipe associée en épidémiologie des cancers professionnels (Team grant); Institut de la recherche en santé et sécurité du travail (IRSST); \$1 120,000; 1982-85.
12. Formaldehyde et cancer; IRSST; \$9,500; 1983.
13. Retrospective cohort study in the Montréal fur industry; IRSST; \$34,019; 1983-85.
14. Statistical analysis of a case-control study designed to discover occupational carcinogens; NHRDP-H&W Can.; \$484,022; 1985-87.
15. Completion of chemical coding of exposures in a case-control study designed to discover occupational carcinogens; IRSST; \$102,180; 1986.
16. Risks of cancer due to exposure to asbestos in a range of occupations; IRDA; \$61,206; 1986-87.
17. Biological estimation of exposure: a tissue registry for the identification and quantification of occupational carcinogens; NCIC; \$3,500*; 1986-87; (P.I. Dr B. Case)
18. Development of a proposal to study cancer risk and non-occupational exposure to asbestos; H&W Can.; \$29,500; 1987-88.
19. Evaluation of cancer risk and occupational exposure to formaldehyde; H&W Can.; \$30,000; 1987-88.
20. A genetic-epidemiologic study of breast cancer; NIH-NCI; \$90,945(US)*; 1987-92; (P.I. Dr. R. Haile).

21. Scholar award; NHRDP-H&W Can.; \$298,689; 1987-93.
22. An intervention trial to assess the risks of gastro-intestinal illness associated with consumption of treated tap water; NHRDP; \$225,000*; 1987-89; (P.I. Dr P. Payment).
23. Evaluation of cancer risk and occupational exposure to polycyclic aromatic hydrocarbons; H&W Can.; \$29,500; 1988-89.
24. Evaluation of cancer risk and occupational exposure to benzene, toluene and xylene; H&W Can, \$40,000; 1988-89.
25. Health risks due to chrysotile asbestos in the non-occupational environment: a workshop to evaluate a research protocol; H&W Can, \$20,000; 1988-89.
26. A population-based, case-control study of occupational exposure to sulphuric acid and the development of laryngeal cancer: an augmented secondary data analysis; NHRDP; \$11,120*; 1988-89; (P.I. Dr. C. Soskolne).
27. Mortality due to asbestos in the general environment of the Quebec mining areas; H&W Can.; \$130,000; 1989-90.
28. A case-control approach to discovering occupational carcinogens: an analysis of data; NHRDP; \$55,508; 1989-90.
29. Continued analysis of a large case control study of many types of cancer: occupational and non-occupational risk factors; NHRDP; \$463,827 1988-1992
30. Risk of cancer due to cigarette smoking - results of a multi-site case-control study; H&W Can.; \$30,000; 1989-90.
31. Étude sur la validité de matrice emploi-expositions multisectorielles; IRSST; \$18,207*; 1990-1992; (P.I. Dr. M. Gérin).
32. Équipe en épidémiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; \$526,297; 1990-1994.
33. Leukemia in children due to parental occupational exposures; NHRDP; \$108,000*; 1990-1994; (P.I. Dr Claire Infante-Rivard).
34. Risk of cancer due to exposure to chlorinated solvents - results of a multi-site case-control study; H & W Can.; \$30,000; 1991-92.
35. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer retrospective assessment of exposure; H & W Can.; \$60,000; 1991-92.
36. Feasibility of epidemiologic methods to investigate health outcomes near waste sites; H & W Canada; \$33,000; 1991-92
37. A pilot study to evaluate the prevalence of hip arthritis in the Montréal urban setting, and an evaluation of methods of recruitment of a population aged 65+; Montréal General Hospital Clinical Epidemiology; \$15,000*; 1991-92; (P.I. Dr. J. Esdaile).
38. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer; mesothelioma ascertainment; NHRDP; \$164,000; 1991-95.
39. Multivariate Regression Analyses of Occupational Risk Factors for Several Types of Cancers; NHRDP; \$128,827; 1992-96.
40. Development of a Job-Exposure Matrix for Use in Epidemiologic Case-Control Studies of Occupational Risk Factors; NHRDP; \$85,003; 1992-95.
41. A prospective epidemiological study of gastrointestinal health effects due to consumption of drinking water. E.P.A. (US)/ NHRDP/ Nat. Water Res. Inst.; \$300,000*; 1993-95. (P.I.: Dr. P. Payment)
42. A population-based, case-control study of occupational exposure to acidifying agents and the development of lung cancer: an augmented, secondary data analysis. NHRDP; \$72,220*; 1993-1995. (P.I. Dr. C. Soskolne).
43. Scholar award; NHRDP-Health Canada; \$126,990; 1993-95.
44. Équipe en épidémiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; \$242,652; 1994-1998.
45. Examen pathologique de cas présumés de mésothéliome recensés chez des femmes depuis 1970 dans des hôpitaux du québec. Health and Welfare Canada. \$30,000. 1994.

46. Cohort Study of a Ten Percent Sample of the Canadian Labour Force. NHRDP; \$12,000*; 1994-97. (P.I. Dr. K. Aronson)
47. A health survey of persons living near the Miron Quarry Sanitary Landfill site, Montréal: a pilot study. NHRDP; \$88,931 ; 1994-95. (P.I. Dr. M. Goldberg)
48. Occurrence of pathogenic microorganisms in water from St Laurent hydrological basin. FRSQ/ NHRDP & St Laurent Vision 2000; 1995-97. (P.I. P Payment)
49. Case-control study of lung cancer and environmental tobacco smoke; Health Canada; \$544,344; 1995-1997.
50. Case-control study of lung cancer and occupational exposures: NHRDP; \$840,000.; 1995–1998.
51. Occupational exposure to solvents and risk of breast cancer; National Cancer Institute of Canada; \$300,000*; 1995-1997. (P.I.: M Goldberg).
52. Scholar Award; NHRDP-Health Canada; \$263,329, 1995-1998.
53. Reanalysis of US data relating general mortality to air pollution; Health Effects Institute; 1998-2000 (P.I. D Krewski)
54. A case-control study of occupational risk factors for lung cancer; Medical Research Council of Canada; \$554,757, 1998-2001
55. Évaluation du risque de cancer du poumon et de mésothéliome associé à l'exposition à l'amiante chez les travailleurs de la région montréalaise; Ministère de la Santé et des Services sociaux; \$12,000. 1998.
56. Feasibility of a case-control study of the association between cell phone use and brain, salivary gland cancer and acoustic neurinoma. International Agency for Research on Cancer; \$12,000, 1998.
57. Inorganic particulate retained dose markers in lung cancer and mesothelioma. CIHR (P.I. Bruce Case) \$66,096. 1999-2003
58. Distinguished Scientist Award, Medical Research Council of Canada; \$330,000; 1999-2004.
59. Évaluation du risque de mésothéliome associé à l'exposition à l'amiante chez les femmes de la région minière; Ministère de la Santé et des Services sociaux; \$27,500. 1999-2000.
60. Program of research in environmental epidemiology of cancer (a national program to enhance capacity to conduct research) PREECAN; National Cancer Inst of Canada; \$1,000,000; 2000-2004.
61. Designing a national research agenda in environmental epidemiology of cancer. Medical Research Council of Canada Opportunities Program; \$40,000; 2000-2001.
62. Multi-centric case-control study of cell phone use and cancer risk in Montréal. CIHR; \$500,000; 2000-2004.
63. Trainee award for: Bernard Rachet, Post-doctoral fellow. PREECAN – NCIC; \$46,750; 2001-2003.
64. Cardiogene: a consortium to explore the gene-environment paradigm of major cardiovascular disorders in human and animal models. Canadian Institutes of Health Research, (P.I. P. Hamet) \$2,632,272; 2001-2007.
65. Canada Research Chair in Environmental Epidemiology. Federal CRC program. \$1,400,000; 2001-2008.
66. Installation of CRC. Canadian Foundation for Innovation. \$312,000; 2002-2004.
67. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 1). Canadian Cancer Society, Prostate Cancer Research Initiative, National Cancer Institute of Canada, (P.I. M-É Parent) \$947,360; 2002-2007.
68. Center for research on environmental etiology of cancer. For the application process. Centre Hospitalier de l'Université de Montréal (CHUM); \$7,000; 2002-2003.
69. Traffic-related air pollution and socioeconomic gradients in the incidence of cancer. CIHR, (P.I. M Goldberg) \$497,000; 2004-2007.
70. Development and validation of new statistical methods for modeling intermediate events in survival analysis. CIHR, (P.I. M Abrahamowicz) \$68,250; 2004-2005.
71. New survival analytic methods for time-dependent exposures in case-control studies, with applications to cancer. CIHR (P.I. K Leffondré) \$52,791; 2004-2007.
72. Trainee award for: Venkata Ramana Kumar, Post-doctoral fellow. PREECAN – NCIC; \$66,000; 2004-2007.

73. Environmental Cancer Research Team. Development grant for the preparation of the full team grant application. CIHR (P.I. J. Siemiatycki) \$9,500; 2005-2006.
74. Trainee award for: Franco Momoli, PhD student. PREECAN – NCIC; \$25,600; 2005-2006.
75. Occupational and selected non-occupational risk factors for lung cancer: Analysis of a case-control study in Montréal. CIHR (co-P.I.'s: J Siemiatycki & M-É Parent) \$1,920,447; 1999-2011.
76. Development and evaluation of a cost-effective approach for retrospective assessment of occupational exposures in population-based studies (pilot study). Canadian Cancer Etiology Research Network - NCIC (P.I. M-É Parent) \$35,000; 2006-2007.
77. Trainee award for: Aihua Liu, PhD student. PREECAN – NCIC; \$12,600; 2006-2007.
78. Prostate cancer and occupational whole body vibration. Ontario Workplace Insurance Board: Research Advisory Council; Solutions for Workplace Change (P.I. J Purdham); \$140,480; 2006-2008.
79. Guzzo-SRC Chair in Environment and Cancer. Cancer Research Society, \$1,285,000; 2007-2020.
80. INTEROCC: Occupational exposures and brain cancer. NIH (P.I. E Cardis: To support the analysis of the occupational component of an international case-control study involving 13 countries and coordinated at the International Agency for Research on Cancer of the WHO [France]); \$1,626,757 US; 2008-2010.
81. Development and validation of a lung cancer risk prediction model. NCIC (P.I. I Karp); \$102,099; 2008-2010.
82. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 2). NCIC (P.I.: M-É Parent); \$756,000; 2008-2011.
83. Preparation and development of an epidemiological study of modifiable and genetic factors associated with ovarian cancer risk (pilot project). Ovarian Cancer Canada (P.I.: A Koushik); \$28,330; 2008-2009.
84. SYNERGY - Pooled analysis of case-control studies on the joint effects of occupational carcinogens in the development of lung cancer: Montréal component. German Statutory Accident Insurance (DGUV) (P.I.: A Koushik); \$119,177; 2008-2010.
85. The risk of lung cancer related to occupational and recreation physical activity and to dietary intake of flavonoids. Canadian Cancer Research Society. (P.I.: A Koushik); \$208,317; 2009-2012.
86. A case-control study of modifiable and genetic factors associated with the risk of ovarian cancer. Canadian Cancer Society Research Institute (P.I: A Koushik); \$498,997; 2010- 2013.
87. Occupational and selected nonoccupational risk factors for lung cancer: analysis of a case-control study in Montréal. CIHR (P.I: J Siemiatycki, M-É Parent); \$850,620; 2011-2015.
88. Quebec Research Program for Prostate Cancer Prevention. Cancer Research Society (P.I.: M-É. Parent, P Karakiewics) \$4,728,203; 2011-2015.
89. Extreme weather and maternal-child health: targeting future impacts of climate change. CIHR. (P.I.: N Auger) \$85,333; 2015-2019.
90. Development of an instrument for assessing occupational exposures in cancer case-control studies and its application to cancers of lung, brain, ovary. Cancer Research Society- Programme GRePEC (Groupe de recherche et de prévention en environnement-cancer). (P.I.: J Siemiatycki, M Pollak) \$2,510,890; 2011-2018.
91. Occupational physical activity and lung cancer. (P.I.: V Ho, A Koushik).CIHR. \$75,000. 2017-2018.
92. Analyses of existing Canadian cohorts and databases related to occupational physical activity and lung cancer risk. CIHR. (P.I.: V Ho, A Koushik) \$74,989; 2017-2018.
93. The role of lifestyle factors in ovarian cancer prognosis. Department of Defence – Ovarian Cancer Research Program. (P.I.: A Koushik) \$216,458 USD (est. \$293, 000 CAD); 2015-2017. Extended August 2018.
94. Occupational Exposure to Endocrine Disrupting Chemicals and Colorectal Cancer risk. CIHR (P.I.: V Ho, J Siemiatycki) \$252,450; 2018-2021.
95. Occupational exposures of women: improvement of an existing job exposure matrix to provide gender-specific estimations of exposure. IRSST. (P.I.: V Ho) \$491,484; 2018-2021.